5XCC0 Biopotential and Neural Interface Circuits

Stimulation of neural tissues

Eugenio Cantatore

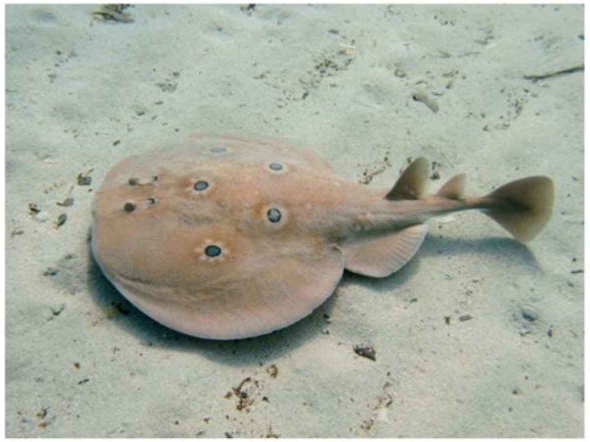
Outline

- Electric stimulation and electrode interfaces
- Different types of stimulation
- Current stimulation: examples of circuit implementation
- Charge balancing

Electric stimulation

- Ancient Greece
- Electrotherapy using torpedo fish
- 30-200V electric disharge

[CC BY 4.0, File:Portrait of Hippocrates from Linden, Magni Hippocratis...1665 Wellcome L0014825.jpg]



[France, Corse, 09.06.2010, cm 50, by Roberto Pillon, fishbase.org/photos/, CC BY]

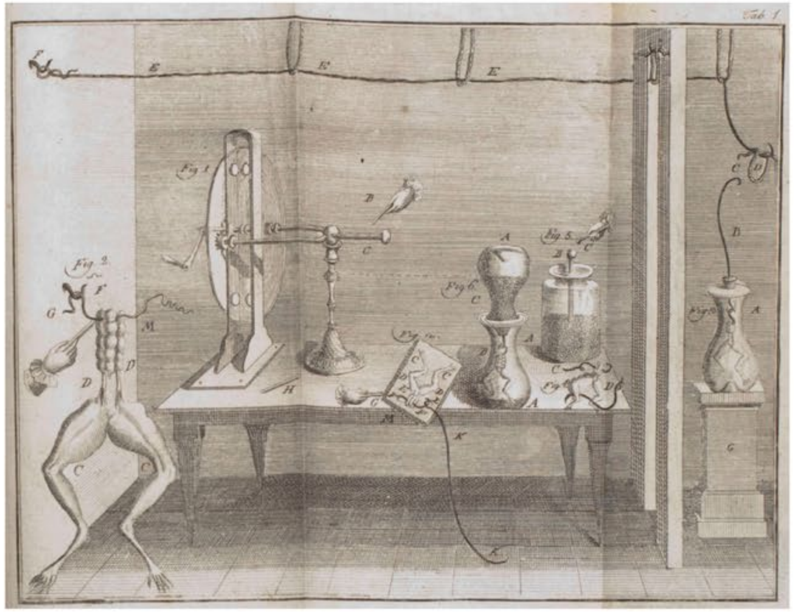
- Arthritis
- Cephalalgia
- Chronic pain
- Epilepsy

M. Haas, M. Ortmanns: “Neural Stimulation Circuits” River Publishers, 2021

Electric stimulation

- 1780 - Galvani's frog leg experiment
  - Accidental discharge of electric charge into a dead animals body
  - Muscle contraction
- Bioelectricity

- A very nice summary of the history of electrical stimulation can be found on:
  - www.ncbi.nlm.nih.gov/pmc/articles/PMC3232561/



[Figure public domain: commons.wikimedia.org/wiki/File:Luigi_Galvani_Experiment.jpeg]

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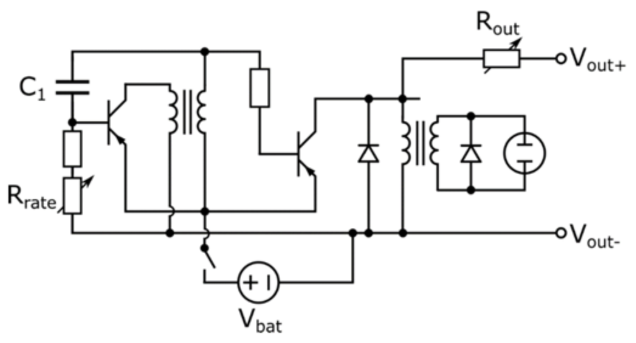
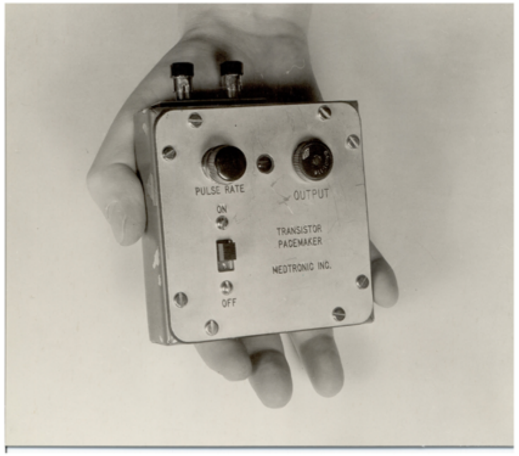
Electric stimulation

- Earl Bakken: american engineer and co-founder of Medtronic
  - 1957: delivered a battery powered metronome to Dr. Lillehei to replace large, wire powered devices
- Those transistor pacemakers were (externally worn) metronomes



c.f. L.A. Geddes, The "missing link" in the history of cardiac pacing [Retrospectroscope], IEEE Engineering in Medicine and Biology Magazine (Volume: 26, Issue: 4, July-Aug. 2007)



Source: "Transistorized Pacemaker", Box 111, C. Walton Lillehei papers, uarc2000-7, University of Minnesota Archives Image is available on the Open Heart online gallery http://gallery.lib.umn.edu/exhibits/show/openheart/item/1879

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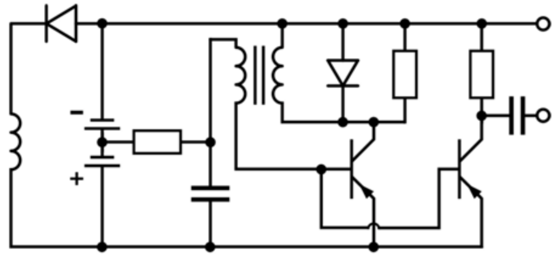
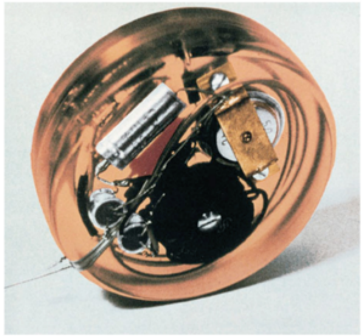
Electric stimulation

- Dr. Rune Elmquist, Swedish engineer
  - Delivered an implantable prototype of a cardiac pacemaker
  - Arne Larsson *May 26, 1915, +Dec. 28, 2001
- 1st pacemaker: Oct. 8, 1958 - working for 8h
  - 2 transistors, 1 NiCd battery, 1 coil, etc..



[c.f. Aquilina O., "A brief history of cardiac pacing", Images Paediatr Cardiol 2006;27:17-81]



[Courtesy Siemens Historical Institute]

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Electric stimulation

- Cardiac pacemaker
  - ½ Mio implants p.a. with >10y lifetime
  - Power, size, functionality, safety, lifetime
  - Intelligent implants vastly determined by IC technology
- Cochlea implants
  - >450,000 worldwide
- Spinal cord stimulators
  - >130,000 worldwide
- Deep brain stimulators
  - >70,000 worldwide
- Vagal nerve stimulators
  - >70,000 worldwide

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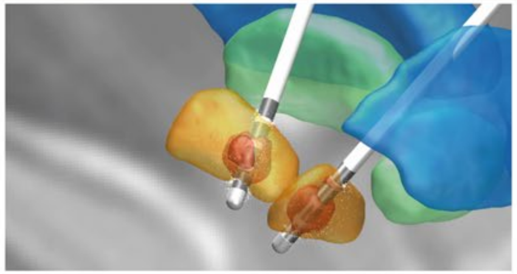
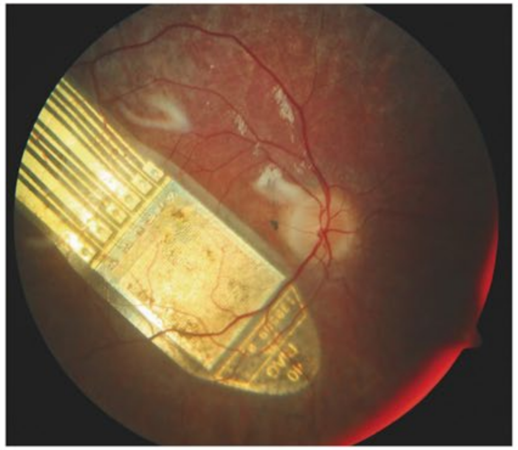
Electric stimulation

- Need excitable tissue
  - Charge transfer elicits response
- Need (conducting) electrical interface to the tissue
- Need charge control
  - Avoid electrolysis
- Needs high area and power efficiency
  - Especially for longterm (battery powered) or highly parallel stimulation



Andreashorn, (commons.wikimedia.org/wiki/File:Deep_brain_stimulation_in_a_Parkinson's_Disease_patient.png), https://creativecommons.org/licenses/by-sa/4.0/legalcode



RETINA IMPLANT Alpha AMS. Source: Universitäts-Augenklinik Tübingen / Retina Implant AG

M. Haas, M. Ortmanns: “Neural Stimulation Circuits” River Publishers, 2021

Electrode interface

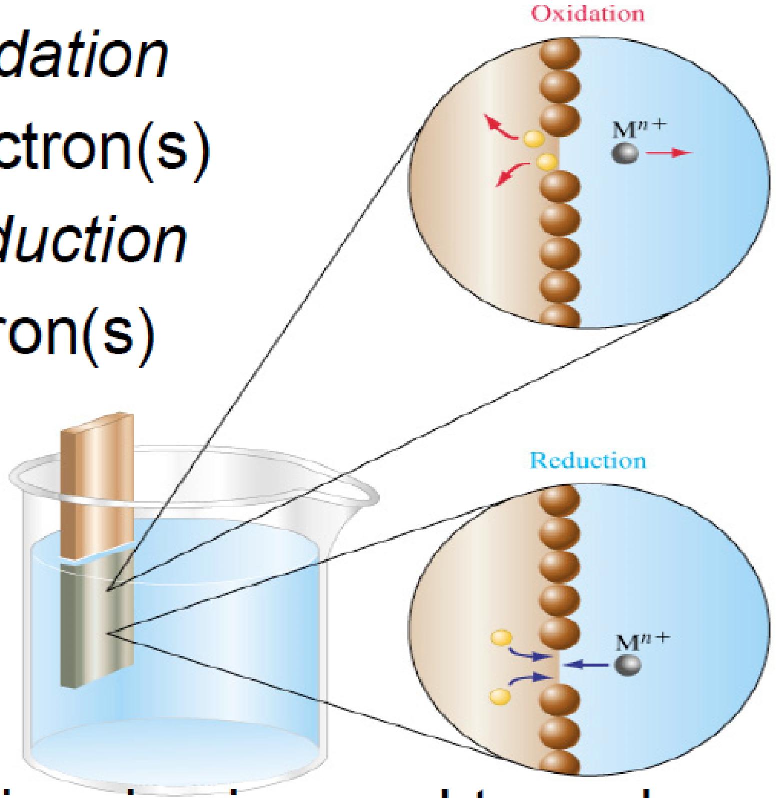
- Potential

$M \rightarrow M^{+n} + ne^{-}$ *Oxidation*

Metal atom loses electron(s)

$M^{+n} + ne^{-} \rightarrow M$ *Reduction*

Metal ion gains electron(s)



Equilibrium:

Current flowing in one direction, i_O, is equal to and cancels out the current flowing in opposite direction.

'Exchange current', i_O.

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Electrode interface

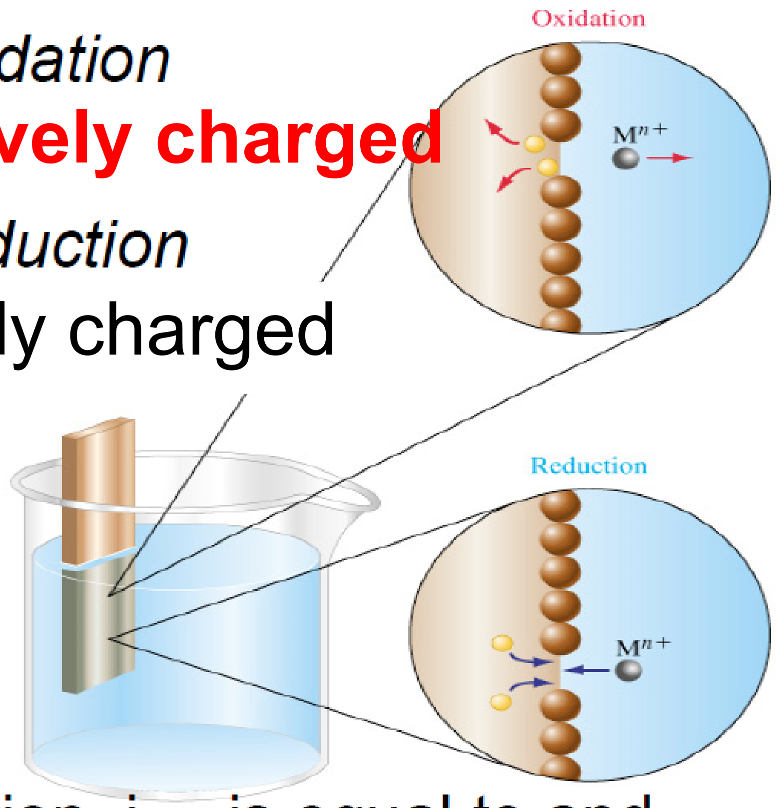
- Potential

$M \rightarrow M^{+n} + ne^-$ *Oxidation*

Metal becomes negatively charged

$M^{+n} + ne^- \rightarrow M$ *Reduction*

Metal becomes positively charged



Equilibrium:

Current flowing in one direction, i_O, is equal to and cancels out the current flowing in opposite direction.

'Exchange current', i_O.

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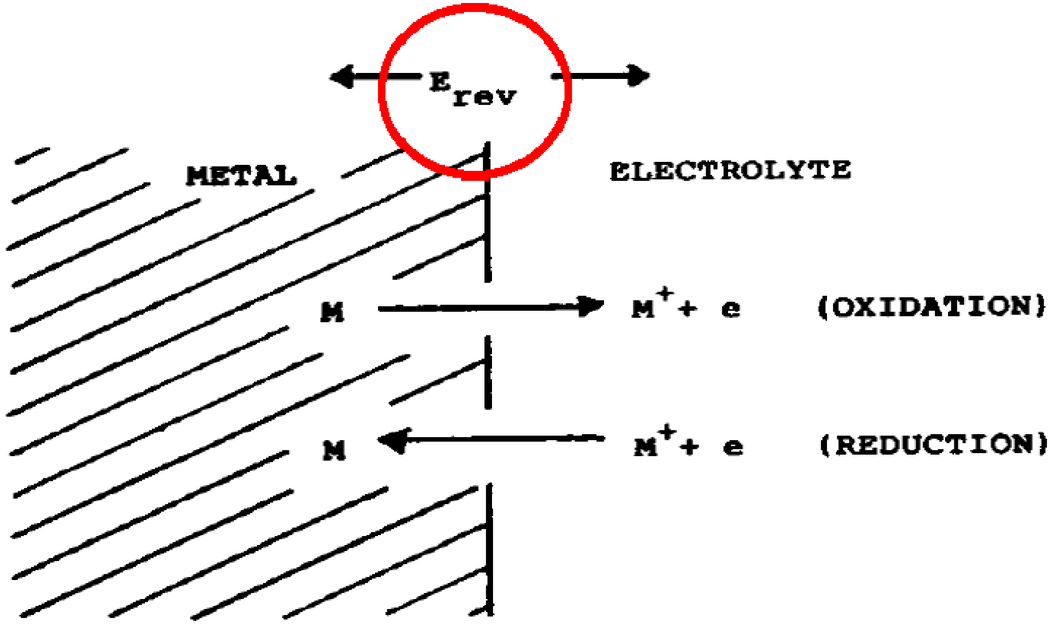
Electrode interface

- Potential at **equilibrium**:



- Total **current is zero, but a potential difference exists**

- Metal is typically negative

- This is called ‘Equilibrium’, ‘reversible or ‘half-cell’ potential

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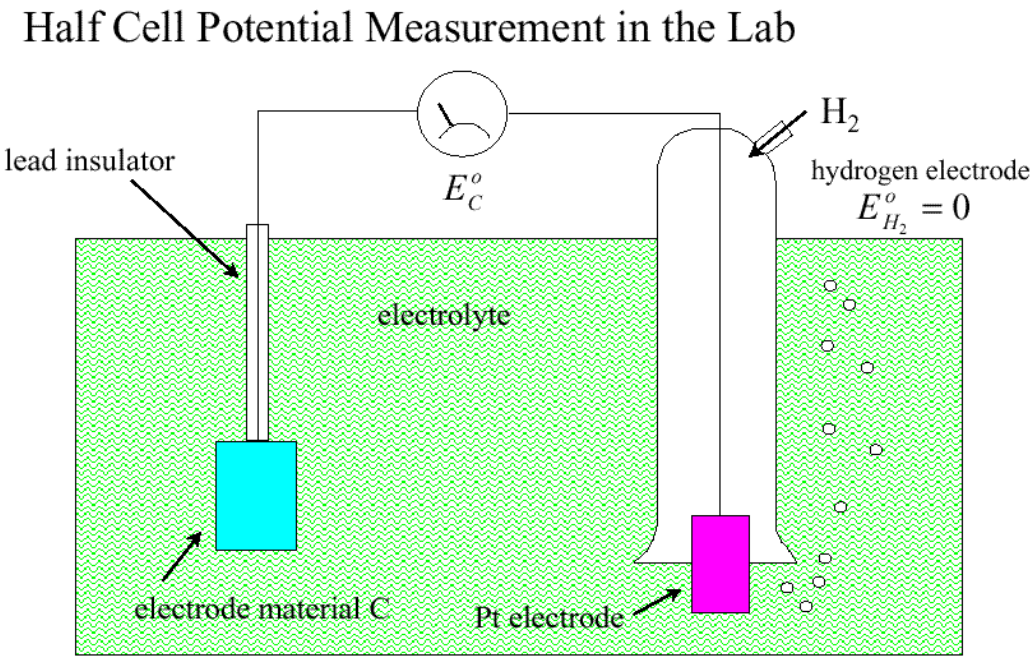
Electrode interface

- Reversible potential:



- A second electrode is needed to measure a voltage
- But then you measure BOTH interface potentials
- Measure electrode potentials relative to Standard Hydrogen Electrode (SHE). SHE Potential is taken as zero

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Electrode interface

- Reversible potential – Nerst equation:

$$E_{rev} = E_o \frac{RT}{NF} \ln\left(\frac{Concentration \quad oxidezed \quad form}{Concentration \quad reduced \quad form}\right)$$

- E_o is standard half-cell potential (relative to SHE)
- R is universal Gas constant,
- n is number of electrons involved in reaction,
- T is absolute temperature (°K),
- F is Faraday constant = eN_A

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Electrode interface

- Reversible potentials

Table 1. Reversible Potentials for Common Electrode Materials at 25 °C[a]

Metal and Reaction	Potential E^V,V
$Al \rightarrow Al^{3+} + 3e^-$	−1.706
$Zn \rightarrow Zn^{2+} + 2e^-$	−0.763
$Cr \rightarrow Cr^{3+} + 3e^-$	−0.744
$Fe \rightarrow Fe^{2+} + 2e^-$	−0.409
$Cd \rightarrow Cd^{2+} + 2e^-$	−0.401
$Ni \rightarrow Ni^{2+} + 2e^-$	−0.230
$Pb \rightarrow Pb^{2+} + 2e^-$	−0.126
$H_2 \rightarrow 2H^+ + 2e^-$	0.000 by definition
$Ag + Cl^- \rightarrow AgCl + e^-$	+0.223
$2\,Hg + 2Cl^- \rightarrow Hg_2Cl_2 + 2e^-$	+0.268
$Cu \rightarrow Cu^{2+} + 2e^-$	+0.340
$Cu \rightarrow Cu^+ + e^-$	+0.522
$Ag \rightarrow Ag^+ + e^-$	+0.799
$Au \rightarrow Au^{2+} + 3e^-$	+1.420
$Au \rightarrow Au^+ + e^-$	+1.680

[a]The metal undergoing the reaction shown has the magnitude and polarity of standard half-cell potential, E_0. Listed when the metal is referenced to the standard hydrogen electrode (3).

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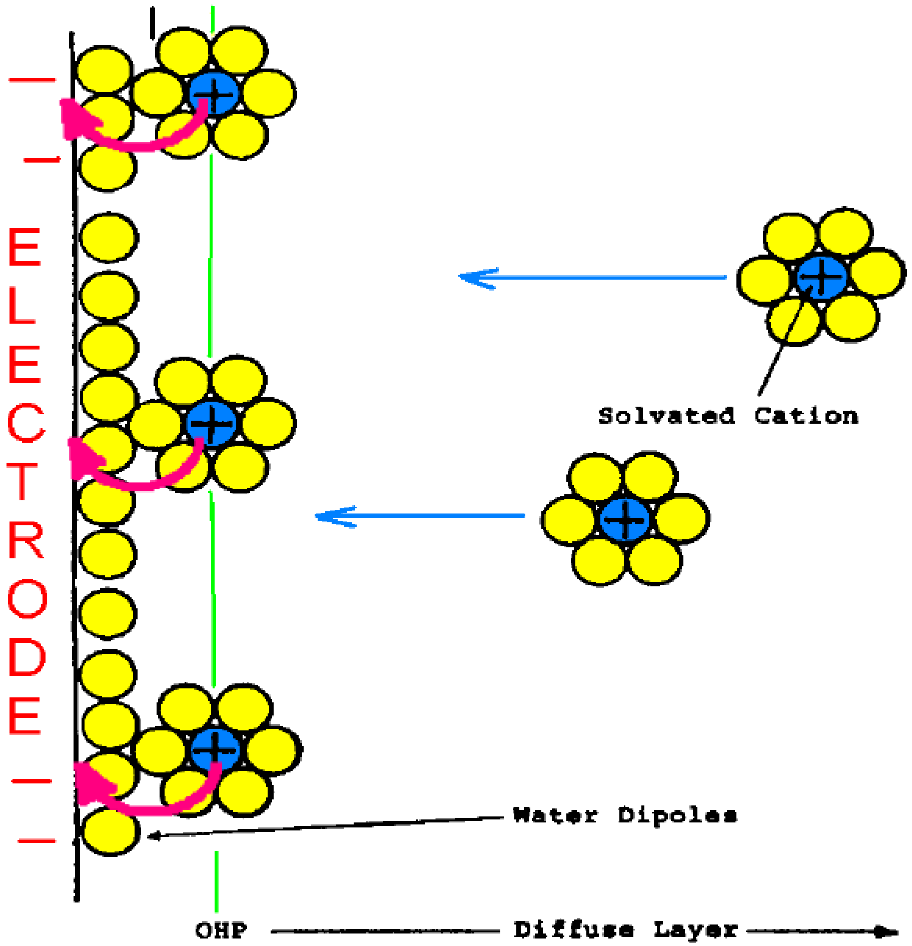
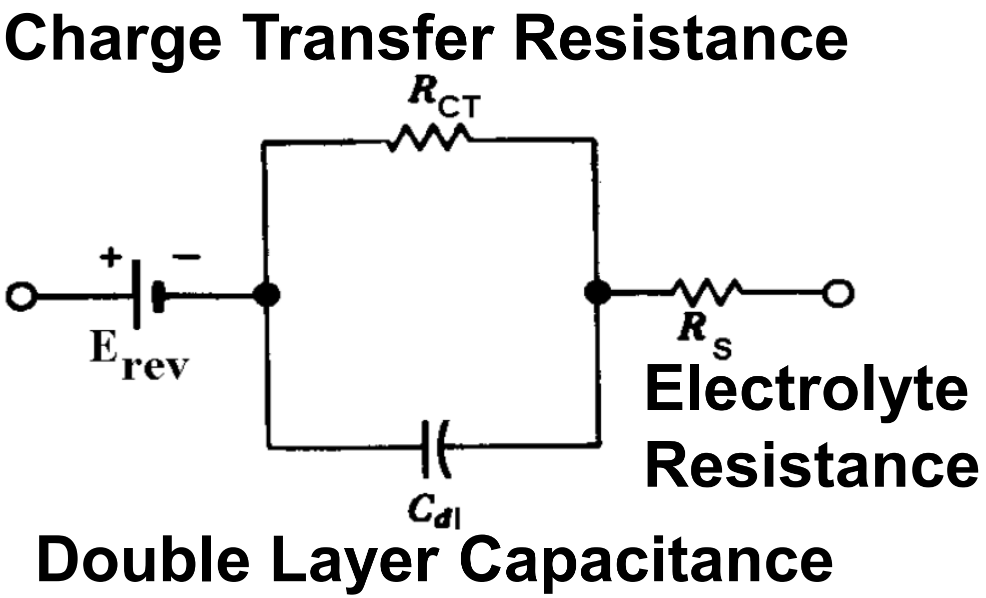
Electrode interface

- Impedance





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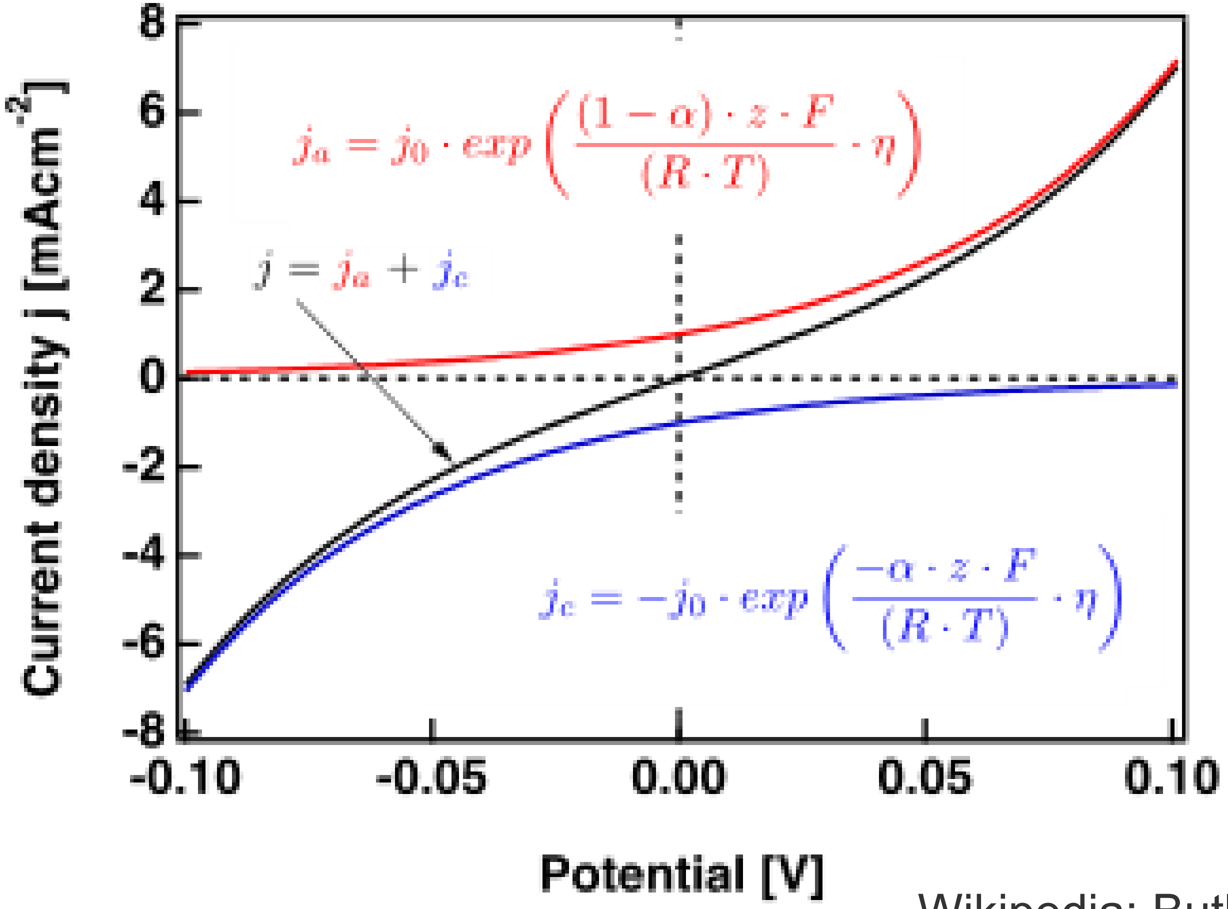
Electrode interface

- Impedance: DC current



Wikipedia: Butler–Volmer equation

Electrode interface

- Impedance: DC current

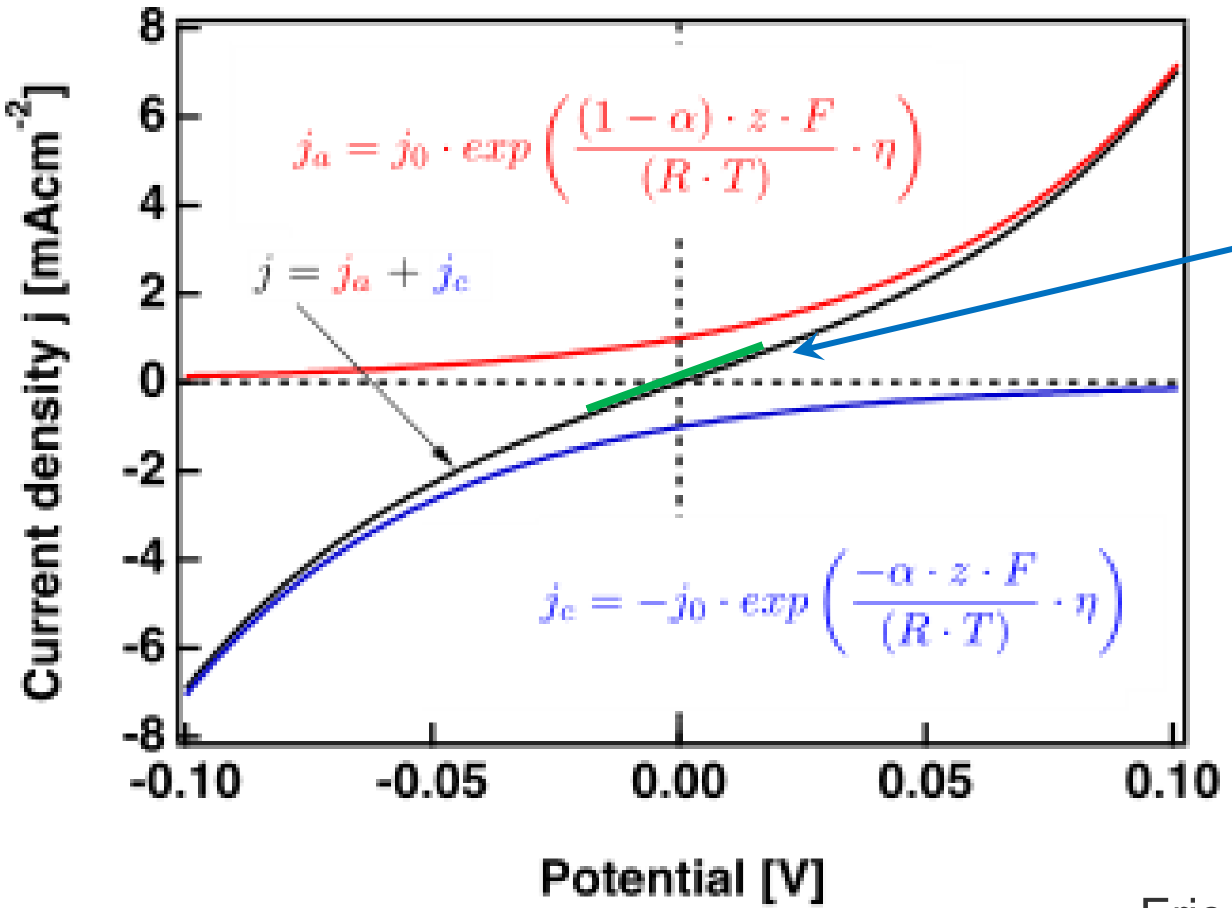
$$j = j_0 \cdot \left\{ \exp\left[\frac{\alpha_{\mathrm{a}} z F \eta}{RT} \right] - \exp\left[-\frac{\alpha_{\mathrm{c}} z F \eta}{RT} \right] \right\}$$

- j : electrode current density, A/m^2 (defined as *i* = *I/A*)
- **j_0 : exchange current density, A/m2**
- η **: overpotential (defined as E-Erev).**
- **E : electrode potential, V**
- **Erev : equilibrium potential, V**
- T : absolute temperature, K
- n : number of electrons involved in the electrode reaction
- F : Faraday constant
- R : universal gas constant
- α_c: so-called cathodic charge transfer coefficient, dimensionless
- α_a: so-called anodic charge transfer coefficient, dimensionless

Wikipedia: Butler–Volmer equation

Electrode interface

- Impedance: small signal Charge Transfer Resistance R_{CT}



$$R_{CT} = \frac{RT}{nF}\frac{1}{i_0}$$

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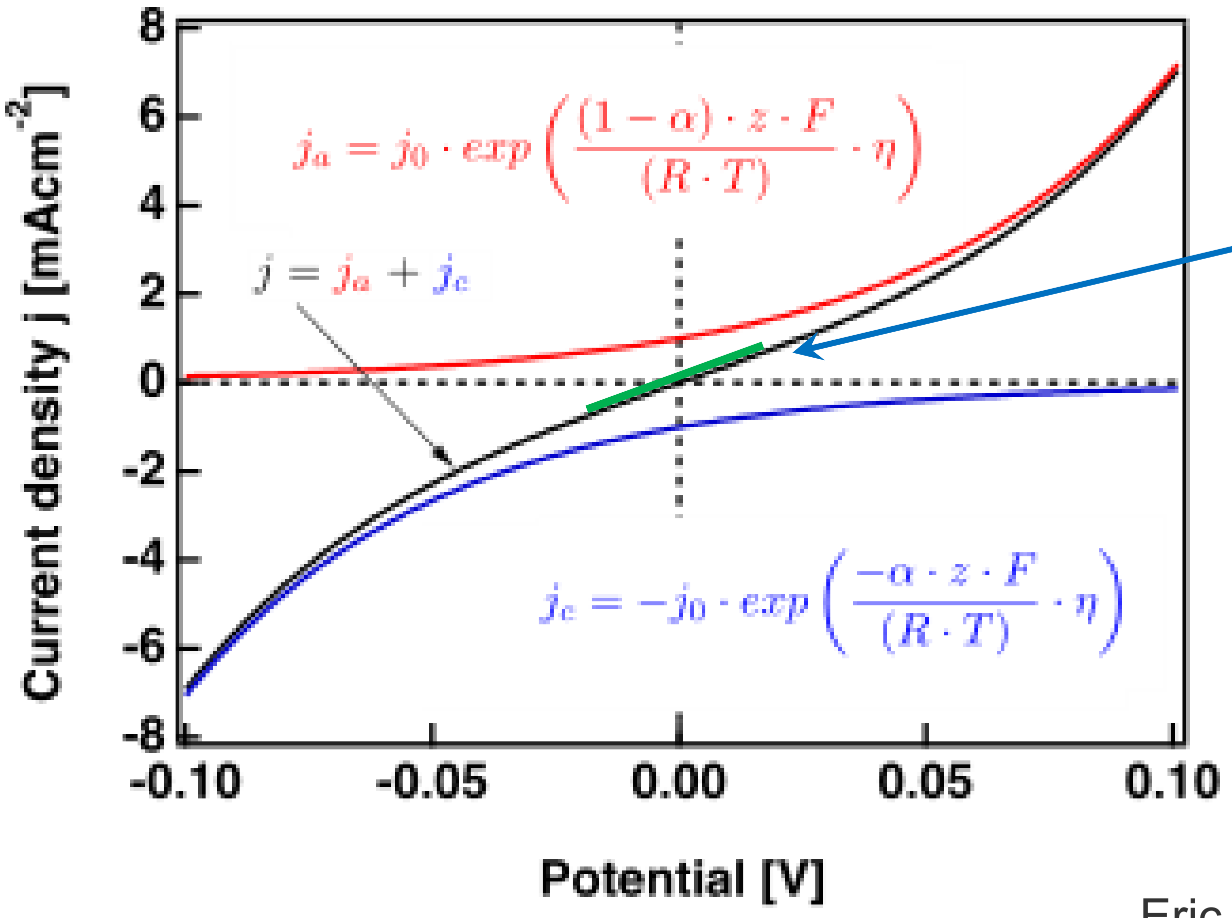
Electrode interface

- Impedance: small signal Charge Transfer Resistance R_{CT}



$$R_{CT} = \frac{RT}{nF}\frac{1}{i_0}$$

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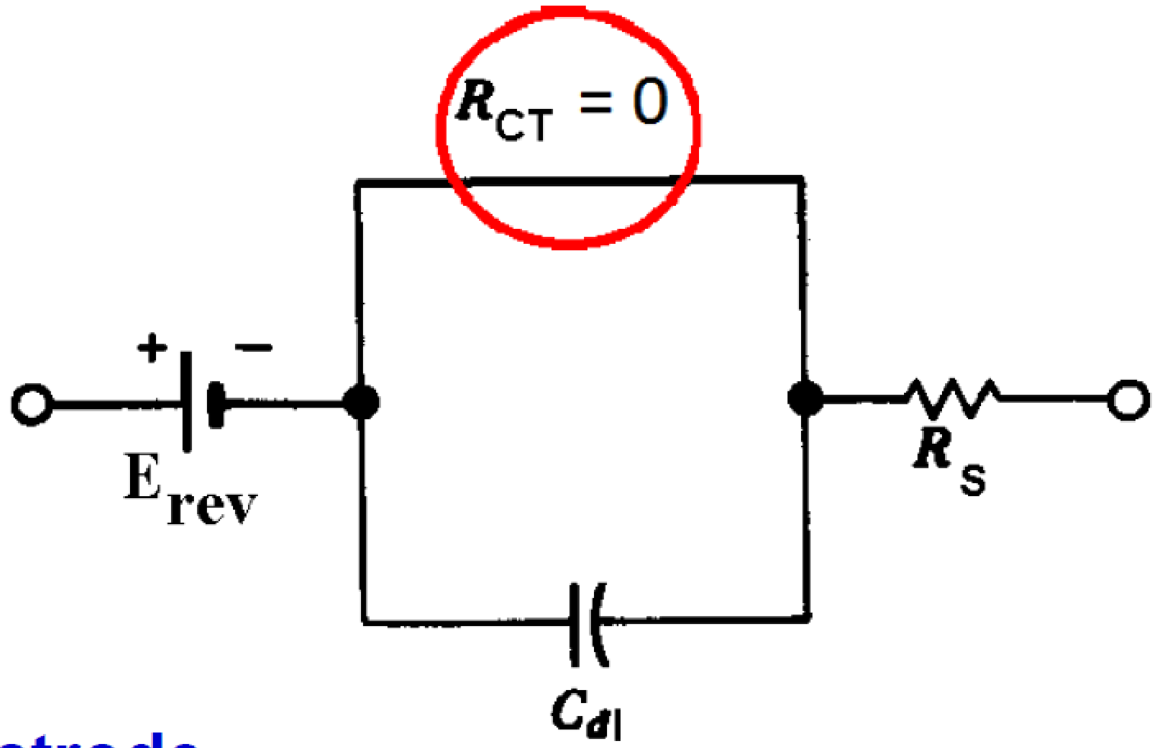
Electrode interface



Surface Electrode

Ideally we want the **biosignal** to flow through the interface **unimpeded**.

We want $R_{CT} = 0$

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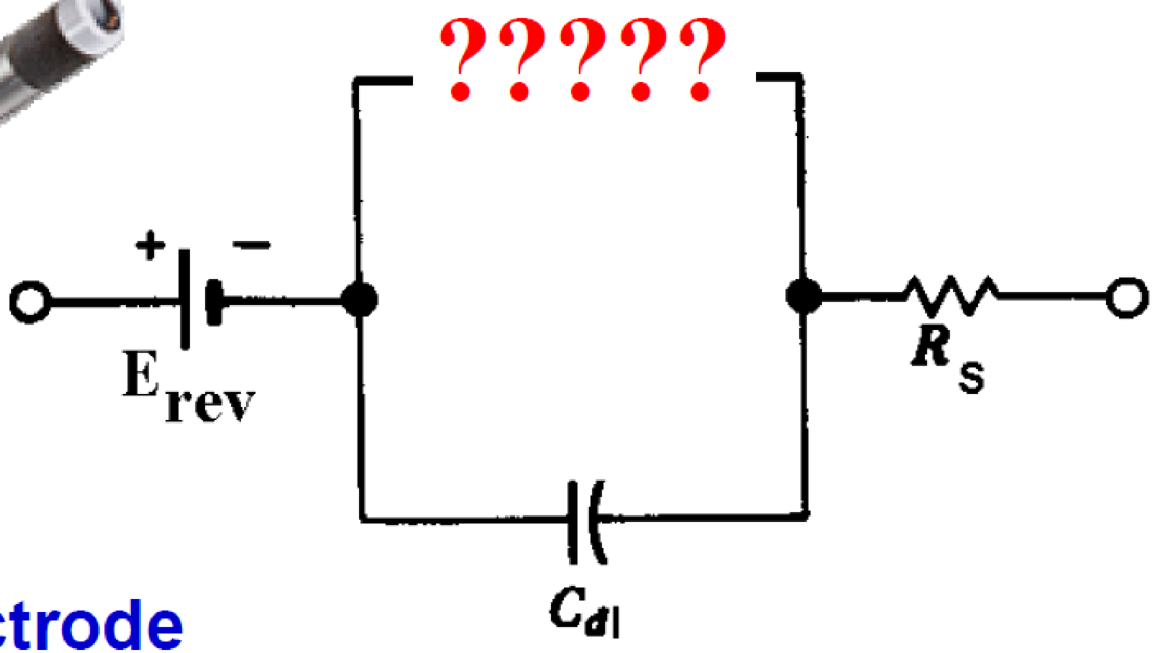
Electrode interface



Implant Electrode

Again we want **biosignal** to flow through interface **unimpeded**. $R_{CT} = 0$

BUT we **do not want electrochemical reactions associated with R_{CT}**. We want $R_{CT} = \infty$

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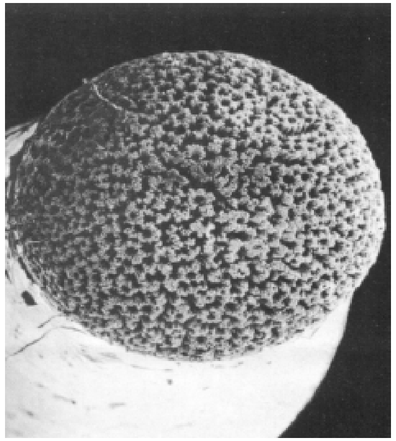
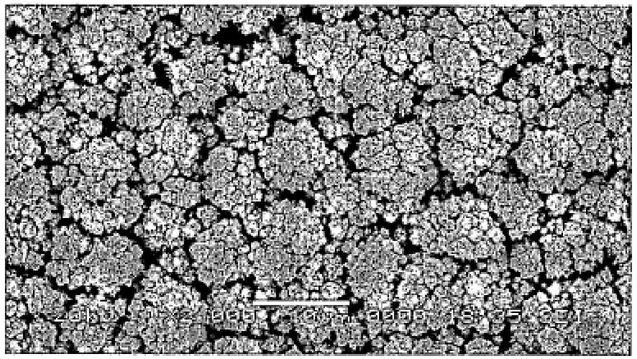
Electrode interface

Implant Electrode

Paradox resolved

- Use **noble metals**: “No” reaction, **biocompatible** ☺, **very large R_{CT}** ☹
- Use of **Surface Roughening:** Increases surface area, **decreases overall impedance**
- Referred to as **“using a depolarising layer”**





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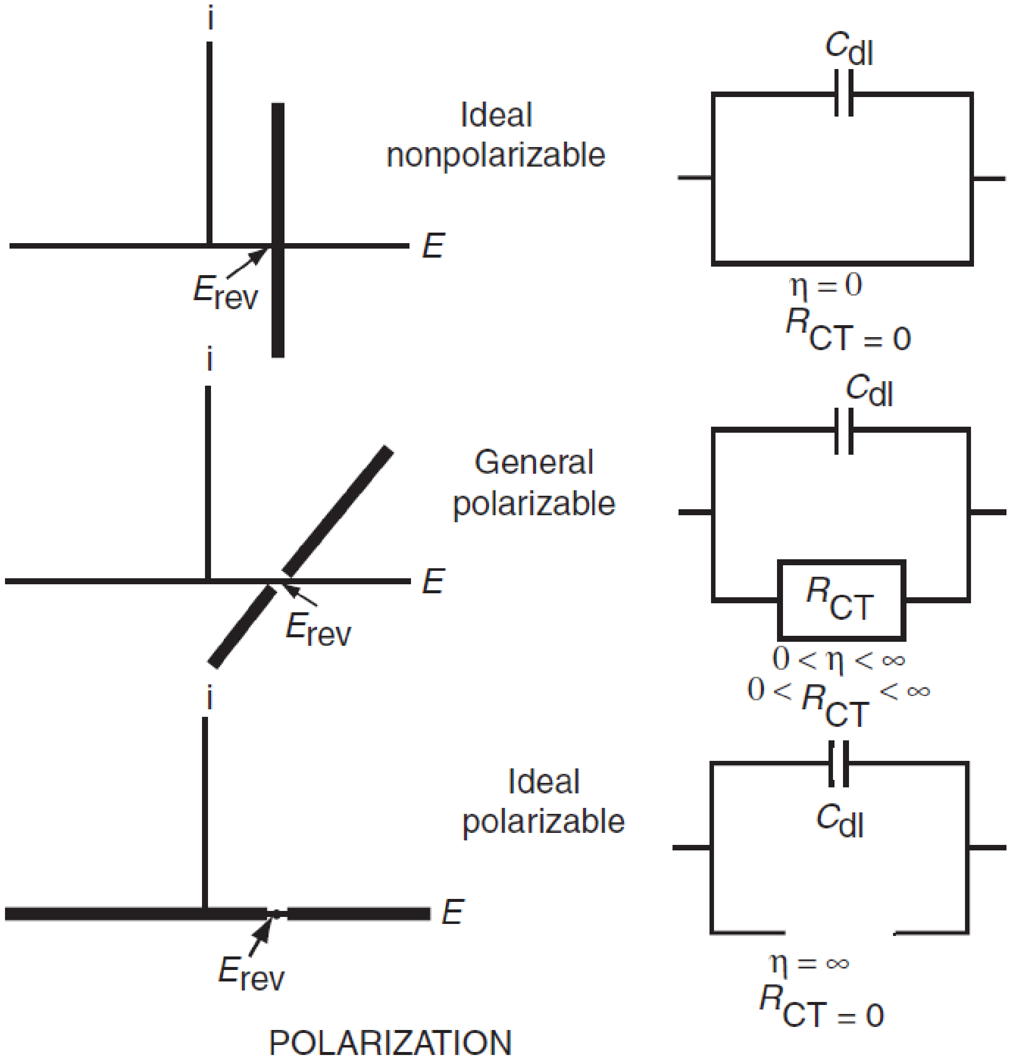
Electrode interface

- Ideal surface electrode
- Real surface electrode
- Ideal biocompatible electrode



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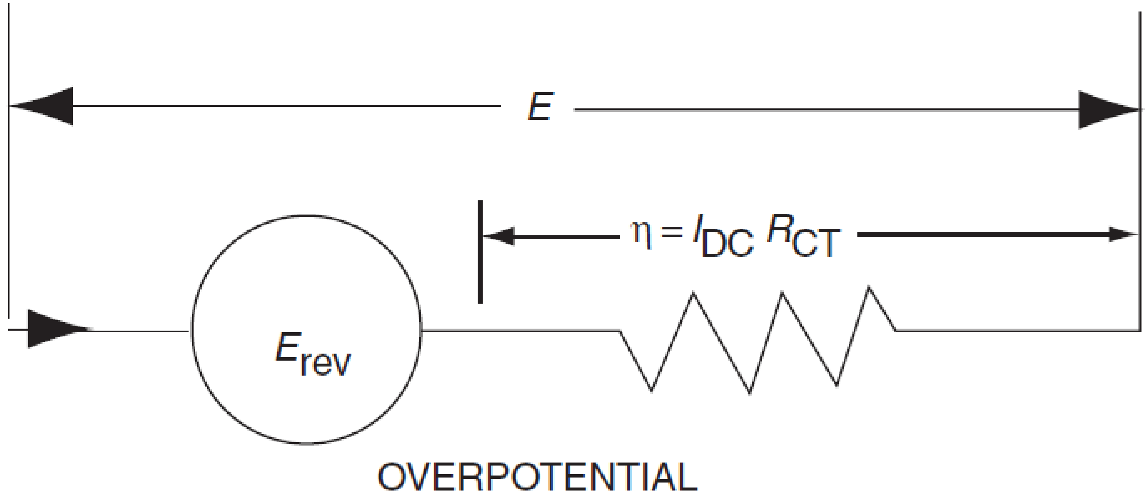
Electrode interface

- Electrode polarisation:

The change of potential of an electrode from its equilibrium potential upon application of dc current



Polarization must be avoided in stimulation (electrolysis):

→ no DC current!!

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Electrode interface

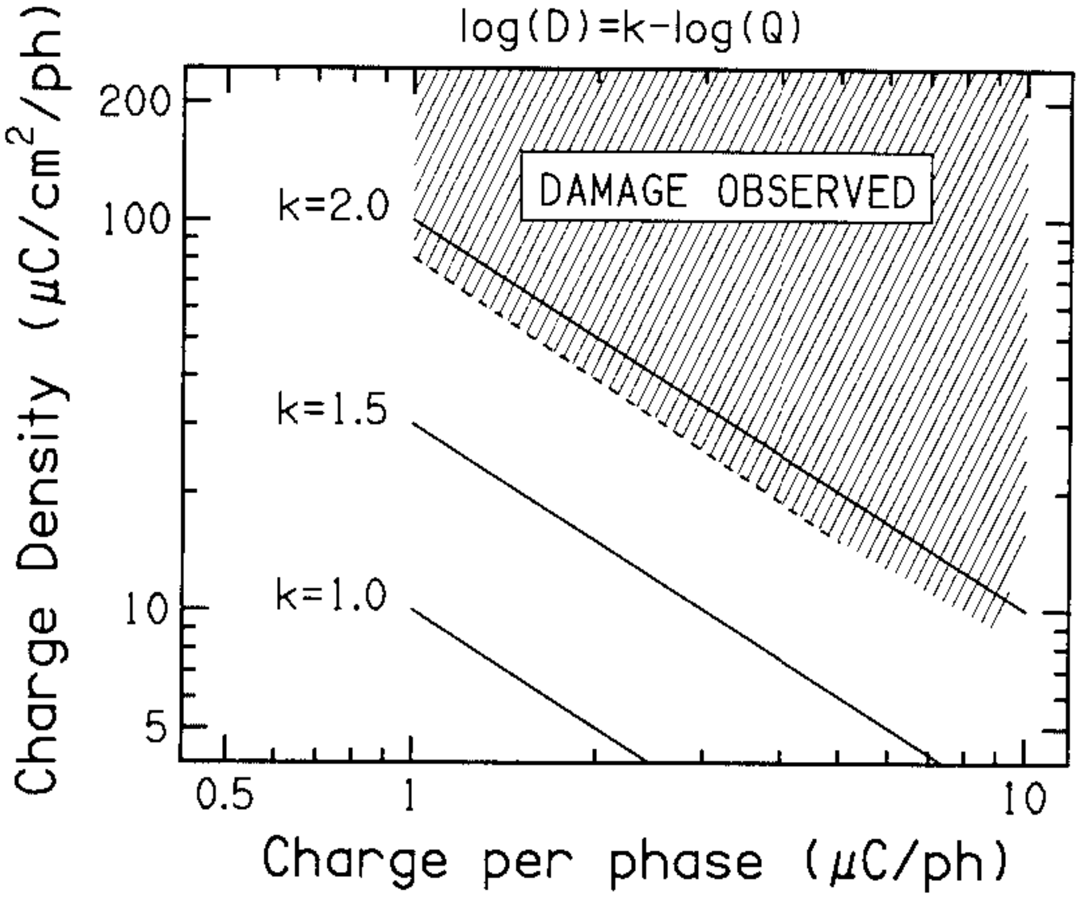
- Empirical limits of safe stimulation

$$\log(D) = k - \log(Q)$$

D = charge density per phase

Q = charge per phase

Phase = half cycle in a charge balanced current pulse: McCreery et al., IEEE Trans. Biom. Eng. 37, 10 (1990)



R. V. Shannon, IEEE Trans. Biom. Eng. 39, 4 (1992)

Outline

- Electric stimulation and electrode interfaces
- Different types of stimulation
- Current stimulation: examples of circuit implementation
- Charge balancing

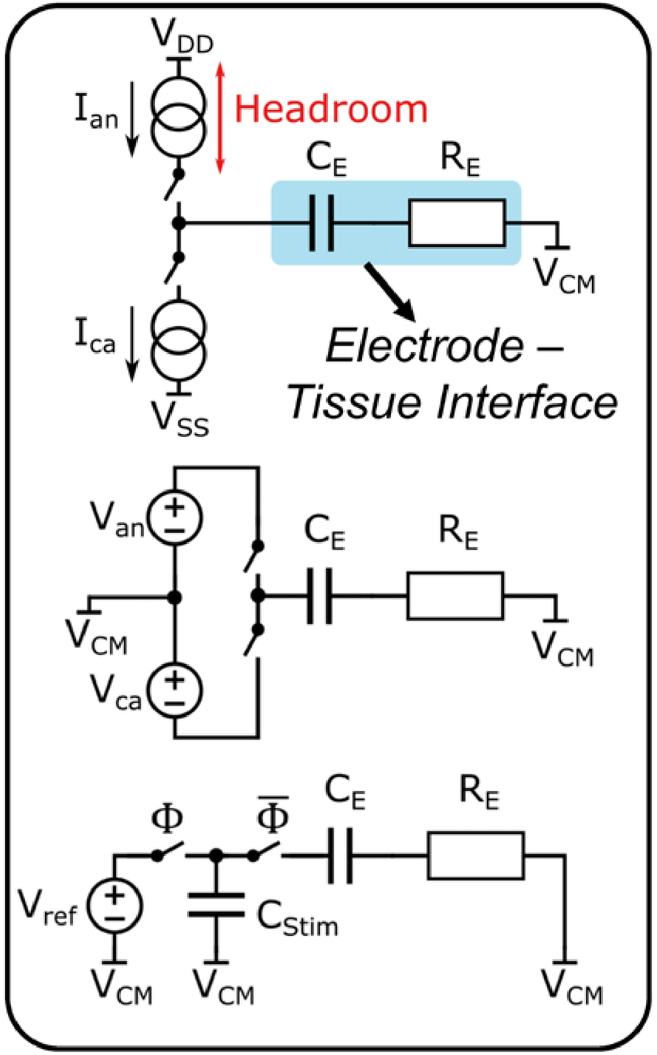
Parameters for effective stimulation

- Strength-duration relationship (threshold current for excitation as a function of the pulse duration)
- Charge-duration relationship (amount of charge for stimulation decreases with shorter pulses)
- Current-distance relationship (more current for farer distance)
- Stimulus polarity (anodic stimulation threshold about 5-8 times higher than for cathodic stimulation).

M. Haas, M. Ortmanns: “Neural Stimulation Circuits” River Publishers, 2021

Different types of stimulation

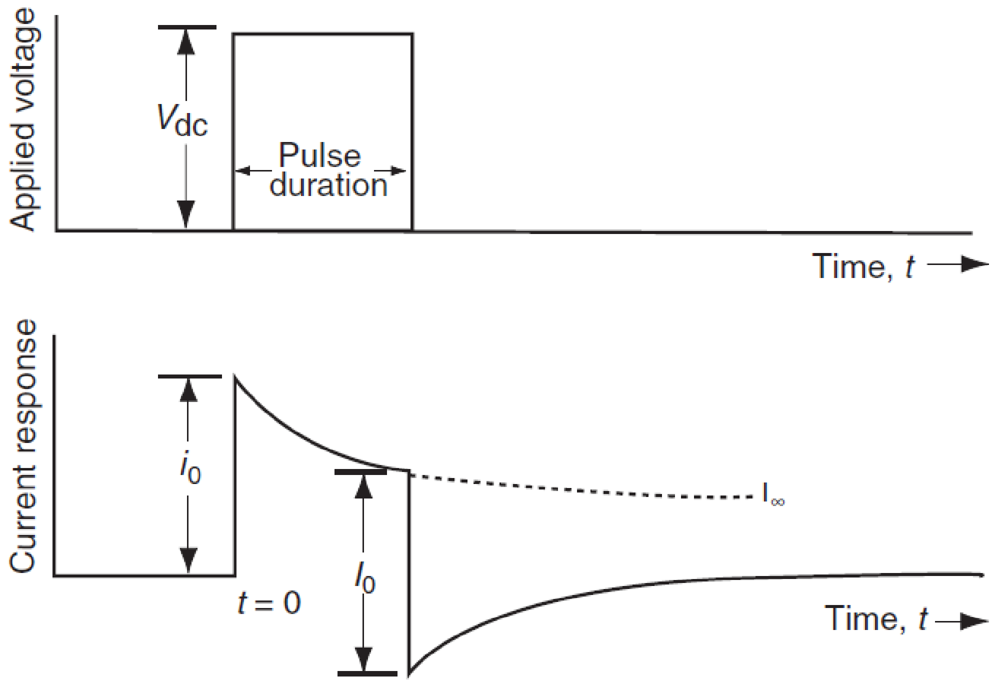
- **Constant current stimulation**
  - ✓ Stimulation charge under control
  - ✓ Stimulation charge not affected by changes in electrode impedance
  - ✗ Low efficiency
- **Constant voltage stimulation**
  - ✓ Highly efficient (stimulation with V_{DD})
  - ✗ Uncontrolled charge transfer
- **Constant charge stimulation**
  - ✓ Highly efficient
  - ✓ Stimulation charge under control
  - ✗ Large external C_{stim}



M. Haas, M. Ortmanns: "Neural Stimulation Circuits" River Publishers, 2021

Different types of stimulation

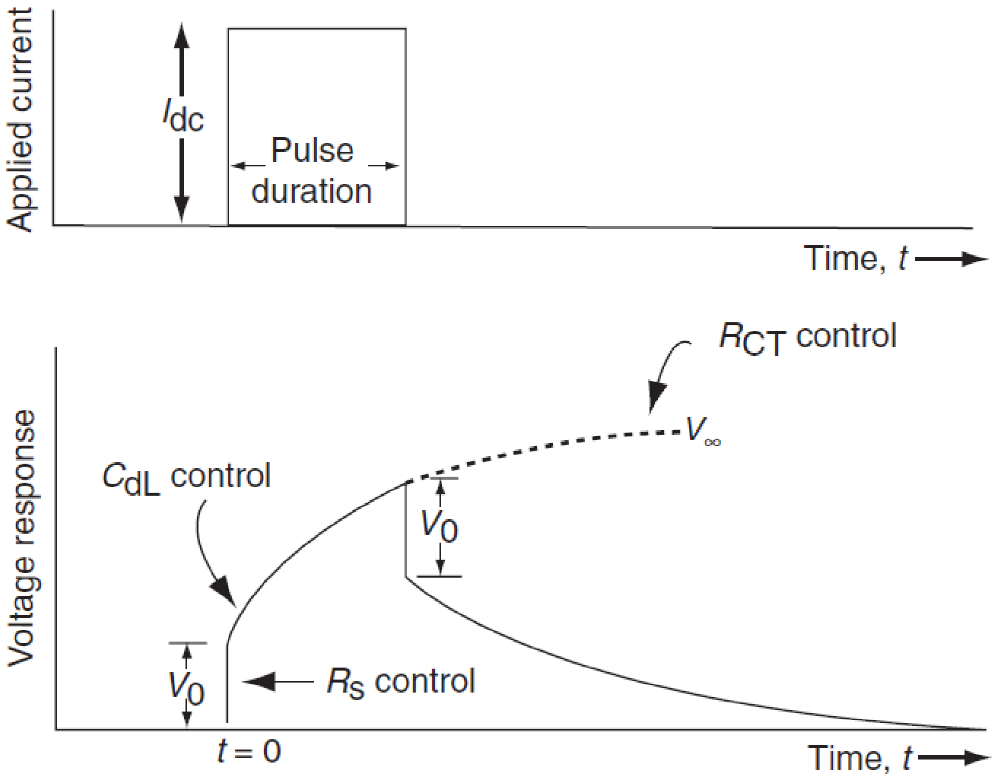
- Voltage stimulation



Eric McAdams, Bioelectrodes, 2006

Different types of stimulation

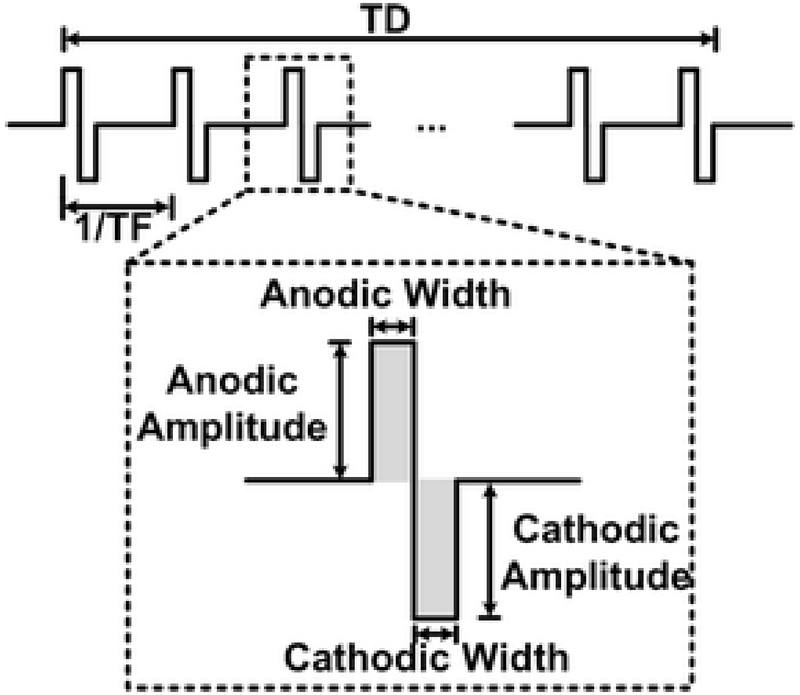
- Current stimulation



Eric McAdams, Bioelectrodes, 2006

Different types of stimulation

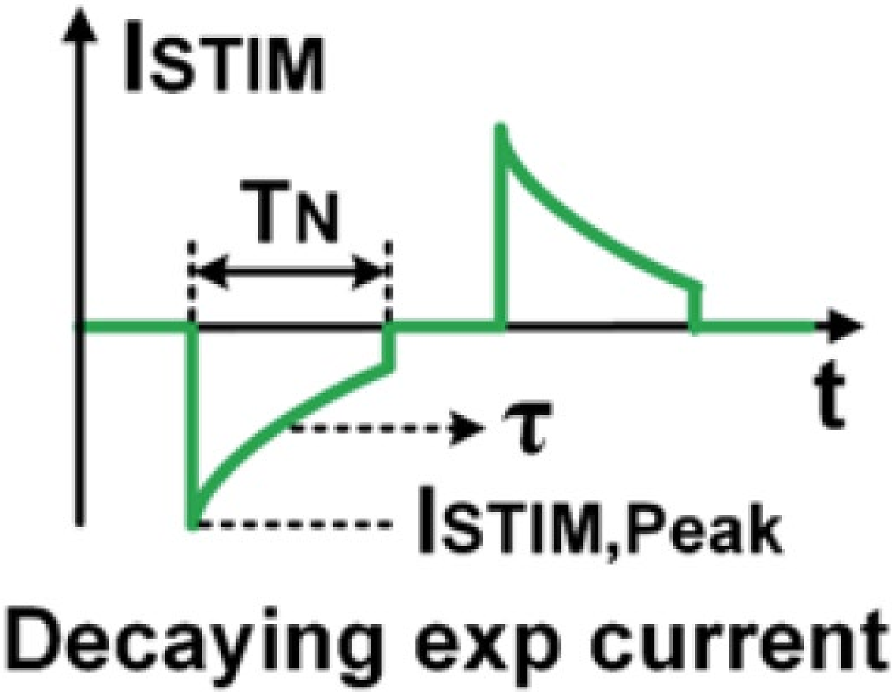
- Current stimulation: typically charge-balanced (zero-DC) pulses



Xiaoran Li et al. BioMedical Engineering OnLine 16, 04 (2017)

Different types of stimulation

- Charge stimulation



M. Haas, M. Ortmanns: “Neural Stimulation Circuits” River Publishers, 2021

Outline

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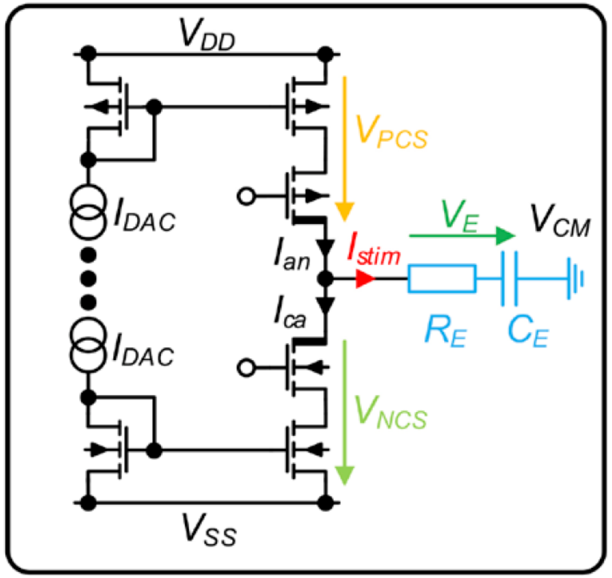
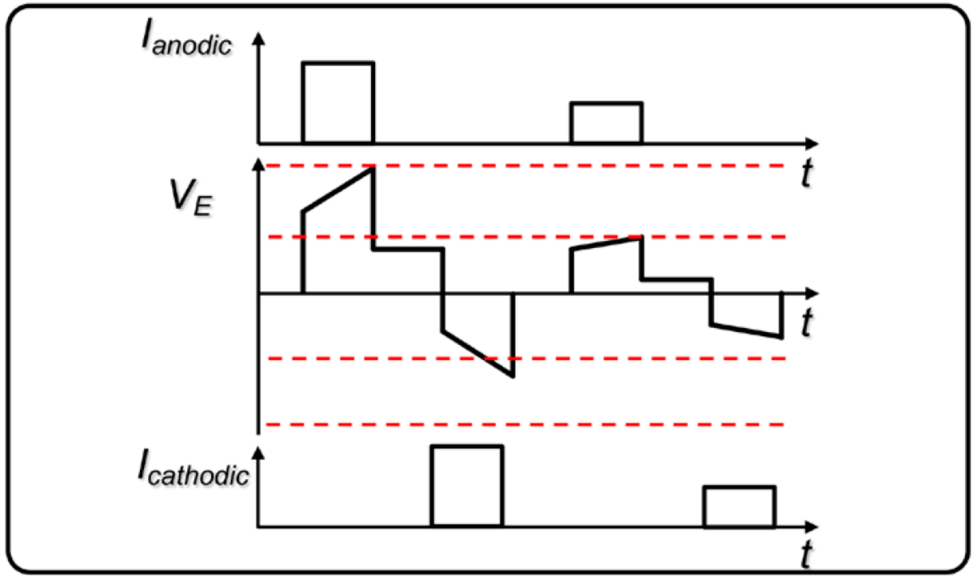
Current stimulation: circuit implementation





- Constant V_{DD} but variable stimulation current and “load”
  ✗ Large fractions of power wasted

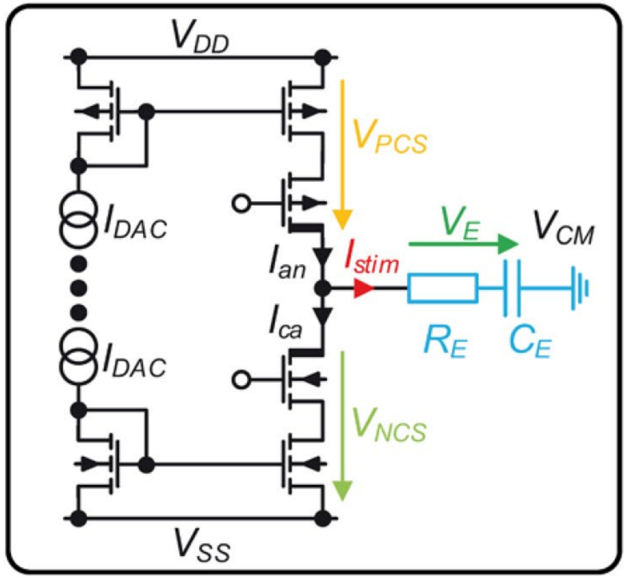
- Voltage compliance ~ $f(I_{max}, Z_E, t_{max})$

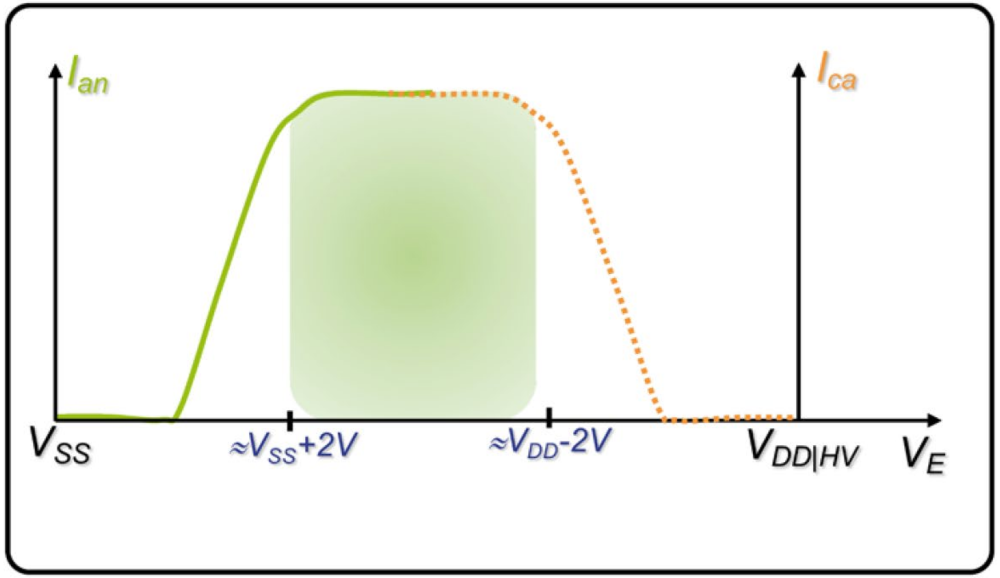
  Z_E=10kΩ+100nF, I_{max}=**500µA**, t_{max}=1ms → **V_{DD}-V_{SS}> 20V** ✓ VC sufficient

  Z_E=10kΩ+100nF, I_{max}=**125µA**, t_{max}=1ms → **V_{DD}-V_{SS}> 5V** 75% wasted

M. Haas, M. Ortmanns: “Neural Stimulation Circuits” River Publishers, 2021

Current stimulation: circuit implementation



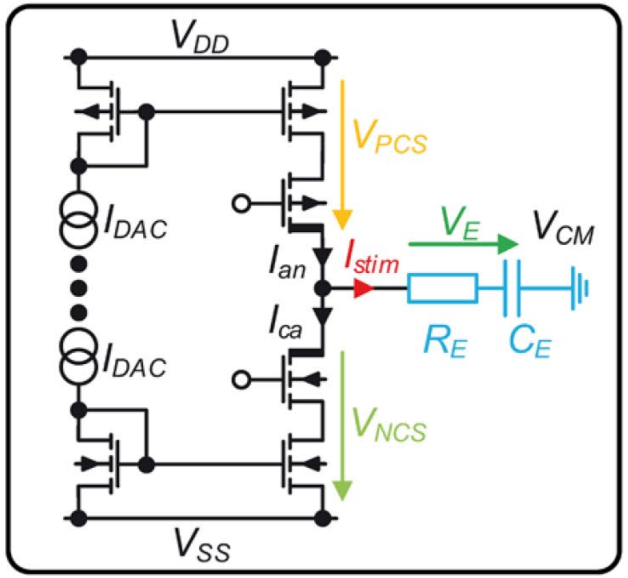


- Current source supply drop $>V_{DSsat}$
  ✗ Large current range (µA … mA) needs large V_{GS} needs large V_{DSsat}

- Example: $V_{SS}+2V < V_E < V_{DD}-2V$ → $\mathbf{V_{DD}-V_{SS}=20V}$ 20% wasted
  → $\mathbf{V_{DD}-V_{SS}=5V}$ 80% wasted

M. Haas, M. Ortmanns: “Neural Stimulation Circuits” River Publishers, 2021

Current stimulation: circuit implementation



- Constant V_{DD} but variable stimulation current and "load"
  ✗ Large fractions of power wasted
- Current source supply drop $>V_{DSsat}$
  ✗ Large current range (μA … mA) needs large V_{GS} needs large V_{DSsat}
- Result:
  ✗ CCS efficiency can drop to <10%

Challenge 1: Constant supply for different loads and stimulation currents
→ **Solution:** Adapt supply to needed compliance – need compliance monitor!

Challenge 2: Overhead voltage of constant current source reduces compliance
→ **Solution:** Make it as small as possible

M. Haas, M. Ortmanns: "Neural Stimulation Circuits" River Publishers, 2021

Example of a current stimulation system

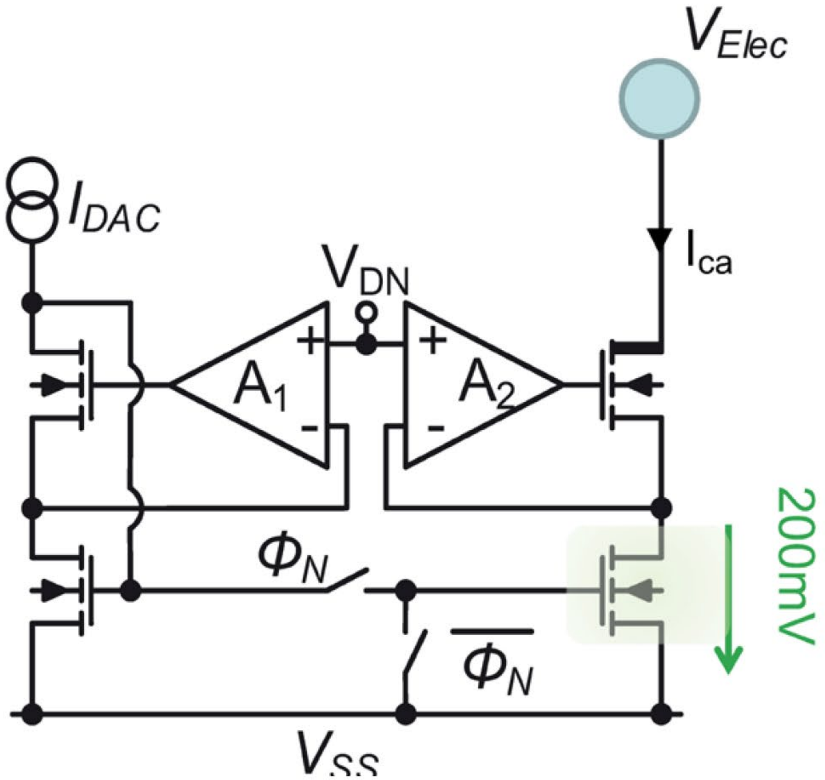
244 IEEE JOURNAL OF SOLID-STATE CIRCUITS, VOL. 47, NO. 1, JANUARY 2012

A Neural Stimulator Frontend With High-Voltage Compliance and Programmable Pulse Shape for Epiretinal Implants

Emilia Noorsal, *Member, IEEE*, Kriangkrai Sooksood, *Member, IEEE*, Hongcheng Xu, *Student Member, IEEE*, Ralf Hornig, Joachim Becker, *Member, IEEE*, and Maurits Ortmanns, *Senior Member, IEEE*

Example of a current stimulation system

- Adaptable supply and low drop
- Triode current mirror
  - Regulated cascode with $A_{1/2}$
  - ✓ $V_{DN|P}$=200mV
  - $P_{A1,2}$ < 1..4μW
  - V_{DDP}=20V, $I_{P/N}$=1-20mA



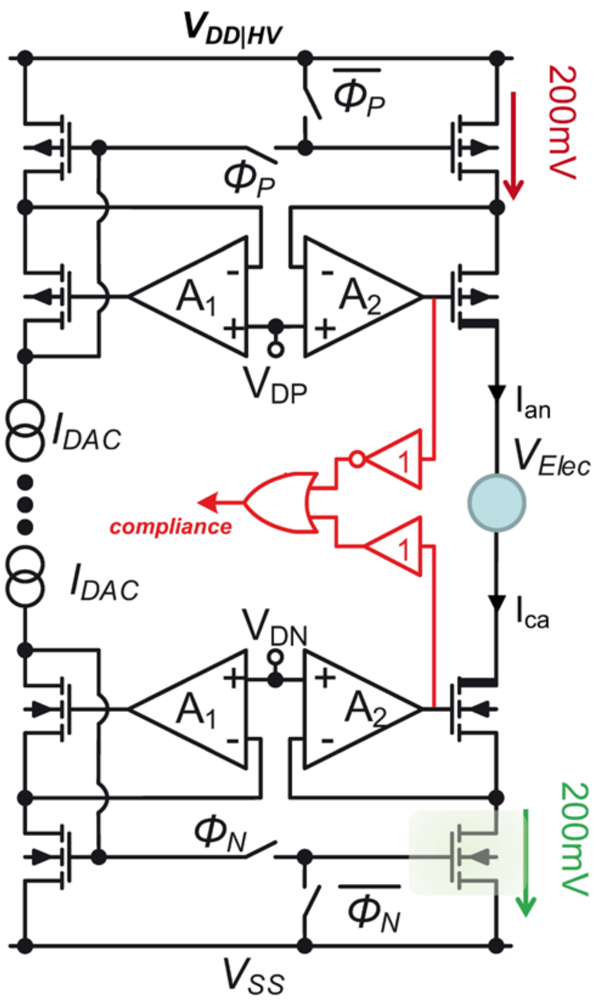
[c.f. Sooksood et al., ISSCC 11]

Example of a current stimulation system

- Adaptable supply and low drop
- Triode current mirror
  - Regulated cascode with $A_{1/2}$
    $V_{DN|P}$=200mV
  - $P_{A1,2}$ < 1..4μW
  - V_{DDP}=20V, $I_{ca/an}$=1-20mA
- Compliance monitor
  Surveys control loop
  Compliance info used to adapt supply V_{DDP}

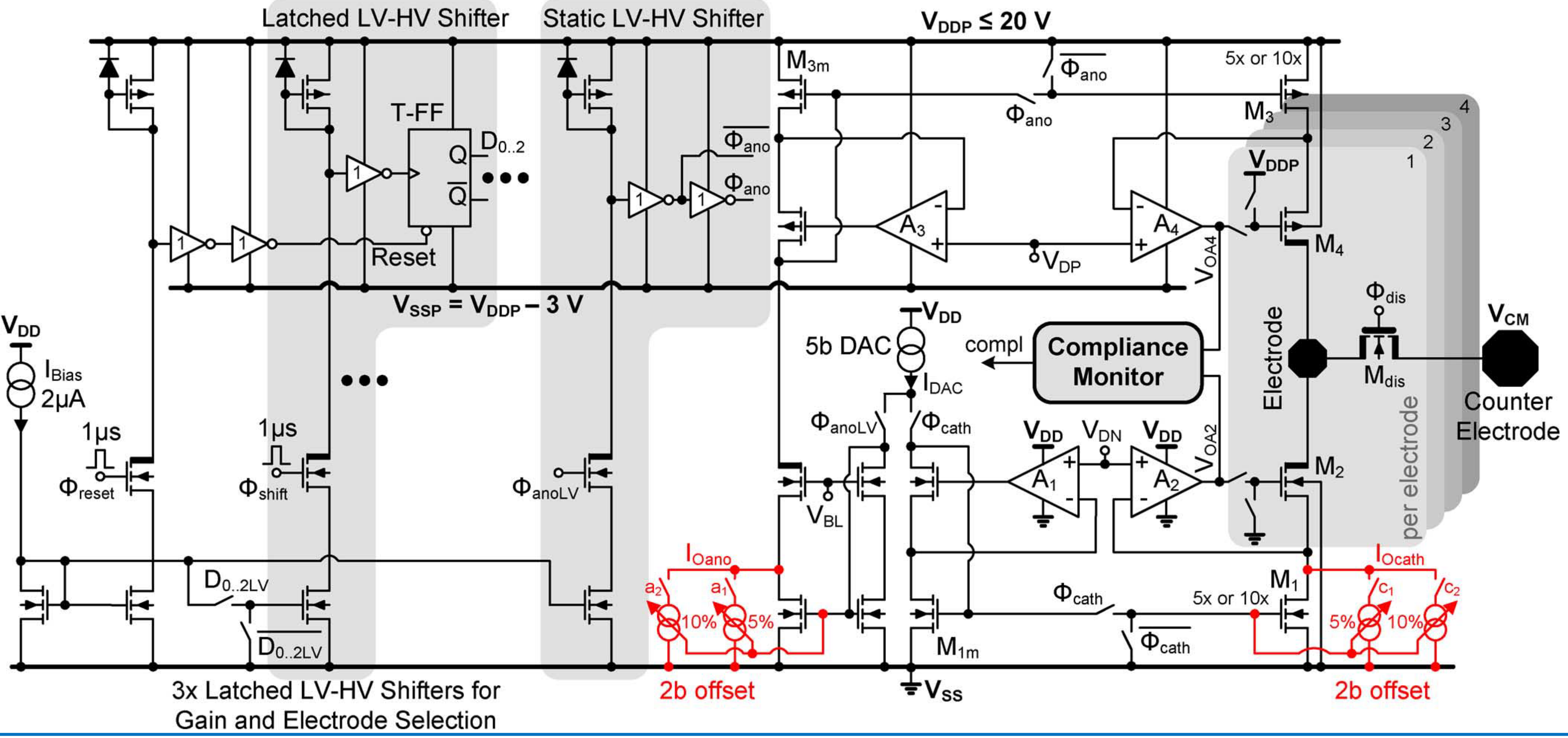
✗ HV mirror bias current still wasted!

[c.f. Sooksood et al., ISSCC 11]



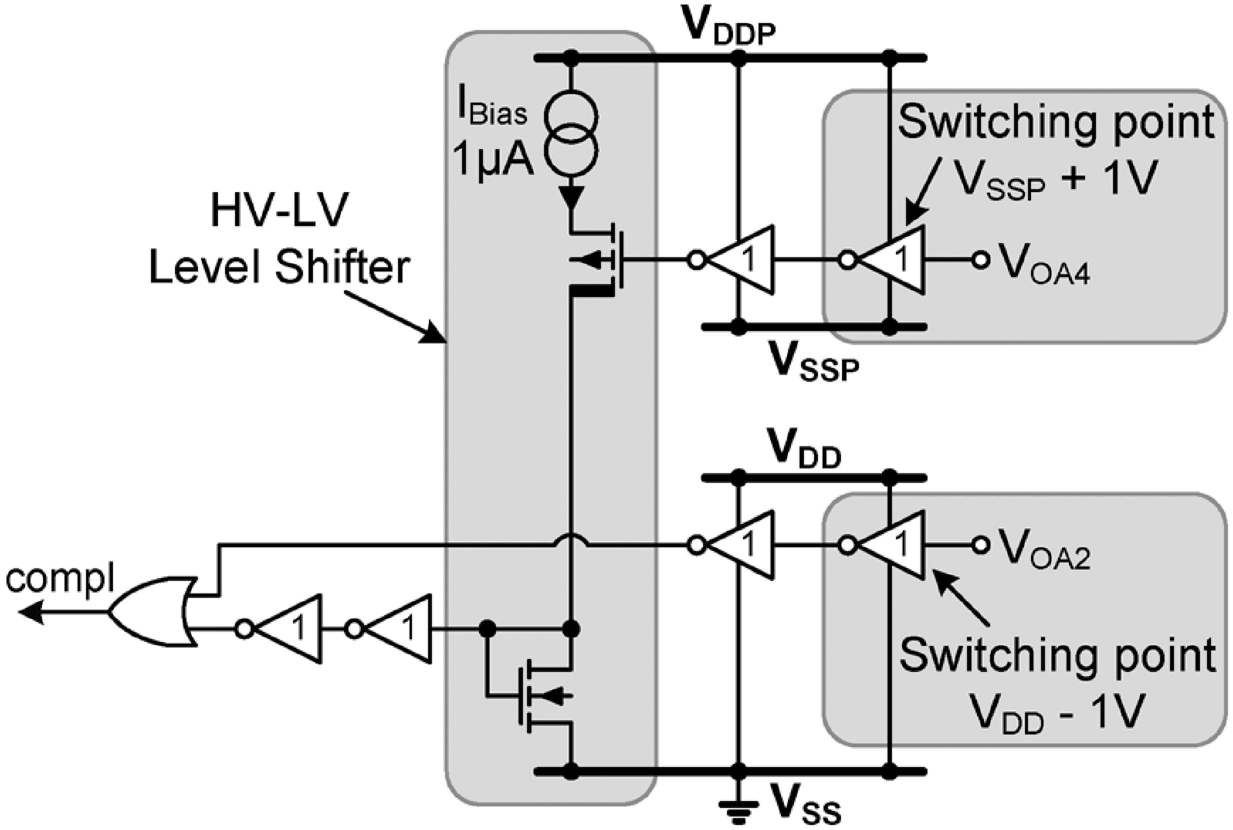
Example of a current stimulation system

- Full system



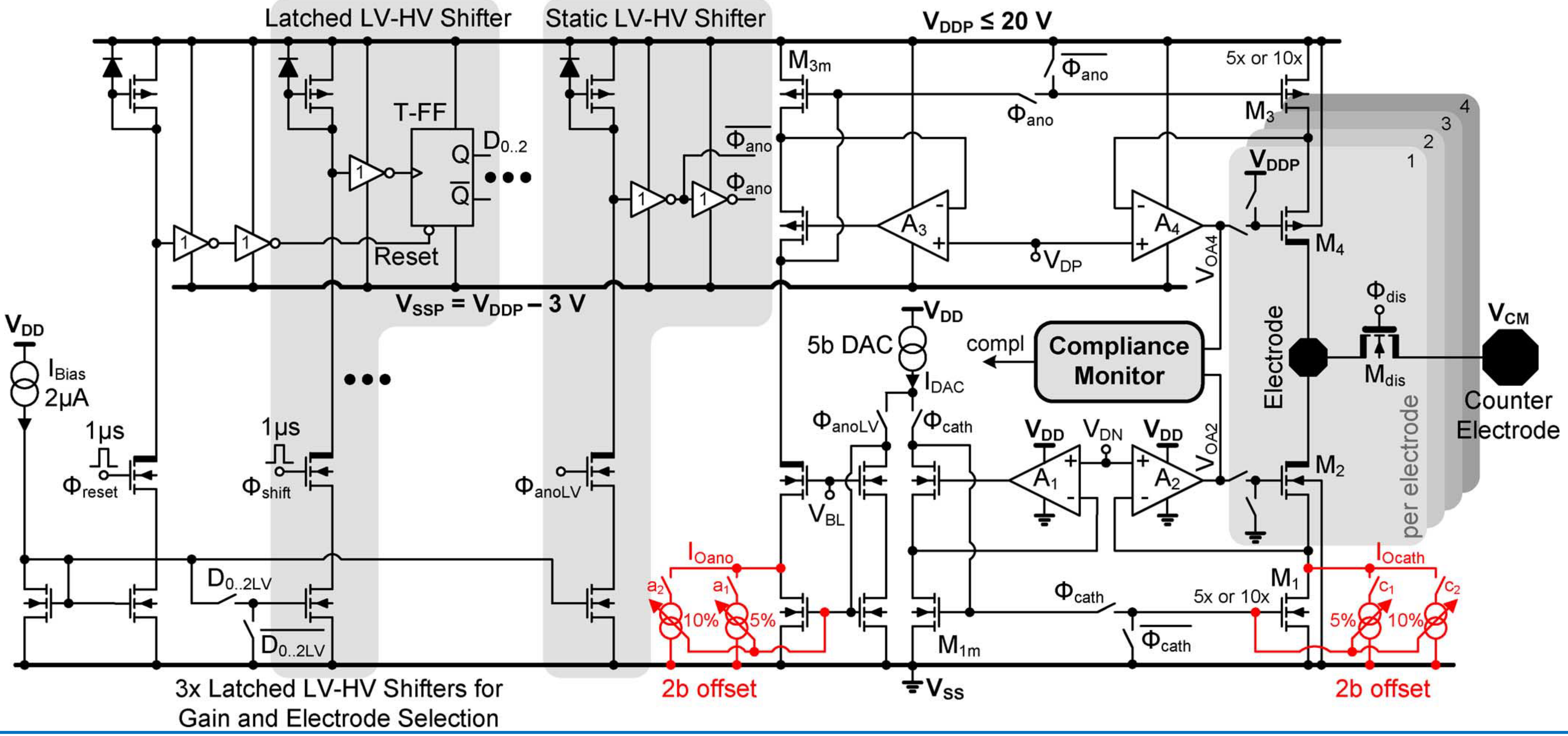
Example of a current stimulation system

- Voltage compliance monitor



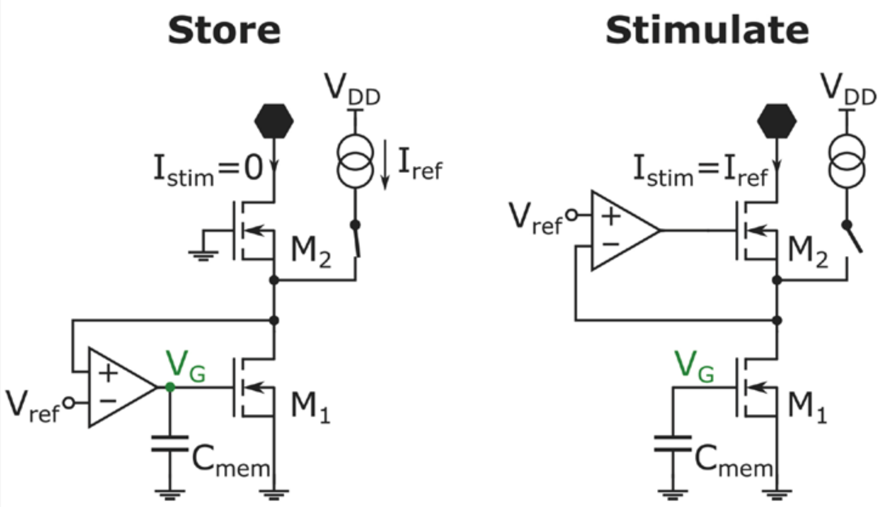
Example of a current stimulation system

- Full system – power hungry HV current mirror input



Example of a current stimulation system

- Possible solution: current copying
  - One DAC feeds N electrodes
    - V_G stored on C_{mem}
    - No static bias current
    - ✗ Regular update
  - This can be merged with the circuit from the last slide
    - "Linear" biased M_1
    - Compliance monitor



[c.f. Shulyzki, Abdelhalim and Genov, ISCAS 2010]
[c.f. Sooksood and Ortmanns, Elec. Letters, 2015]

Example of a retinal stimulation system

- 1600 stimulation sites, AC coupled implant

ISSCC 2008 / SESSION 7 / TD: ELECTRONICS FOR LIFE SCIENCES / 7.5

7.5 A 1600-pixel Subretinal Chip with DC-free Terminals and ±2V Supply Optimized for Long Lifetime and High Stimulation Efficiency

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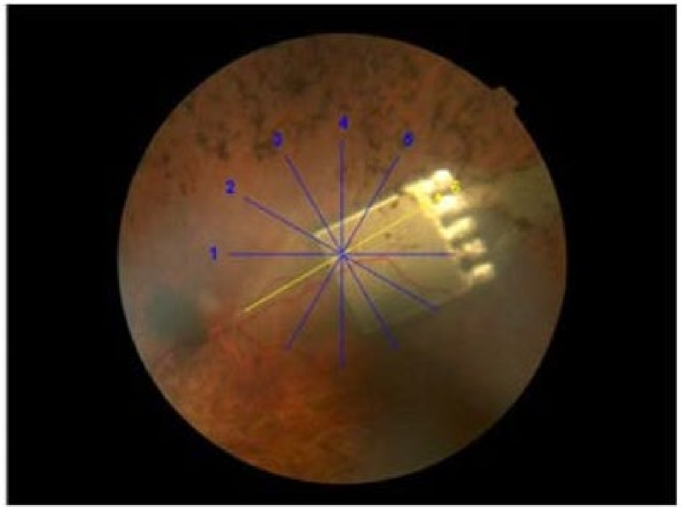
[1]University of Ulm, Ulm, Germany
[2]NMI, Reutlingen, Germany
[3]Retina Implant, Reutlingen, Germany

The *low input impedance amplifiers* (Fig. 7.5.3) use a common gate input stage (M1,2 and M5,6) with GND as reference. The control currents (0 to 200µA) are only positive for ease of the supply design. Input voltage spikes during supply transition are minimized by switching off all control currents (externally) and by a symmetrical design (M1,3 and M5,7), which balances the capacitive coupling from V_{SS} and V_{DD}. Conversion of input current to internal control voltage is done by M11 to M16 and R5. Figure 7.5.4 shows the low parameter sensitivity. The characteristic curve is shifted by M9,10 and R3,4 (output voltage from –2V to +2V with input current from +30µA to +160µA), not to disturb the input

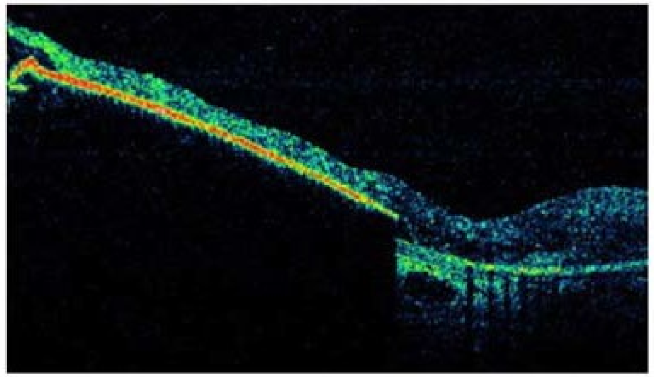
Example of a retinal stimulation system

- 1600 stimulation sites, AC coupled implant

Blind patient grabbing for a plate



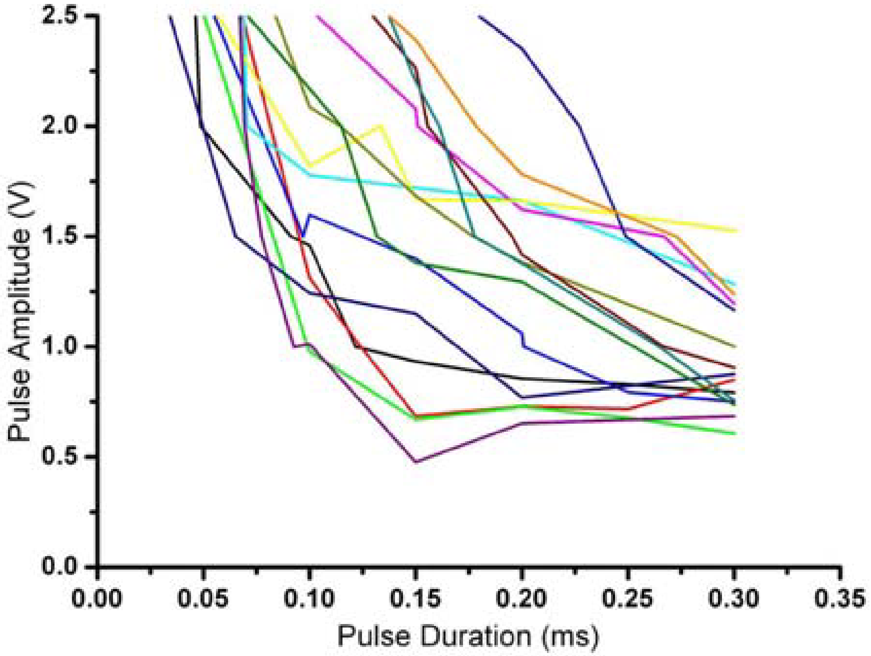
Silicon chip placed beneath retina



Cross section of chip beneath retina in a patient, obtained by optical coherence tomography

Example of a retinal stimulation system

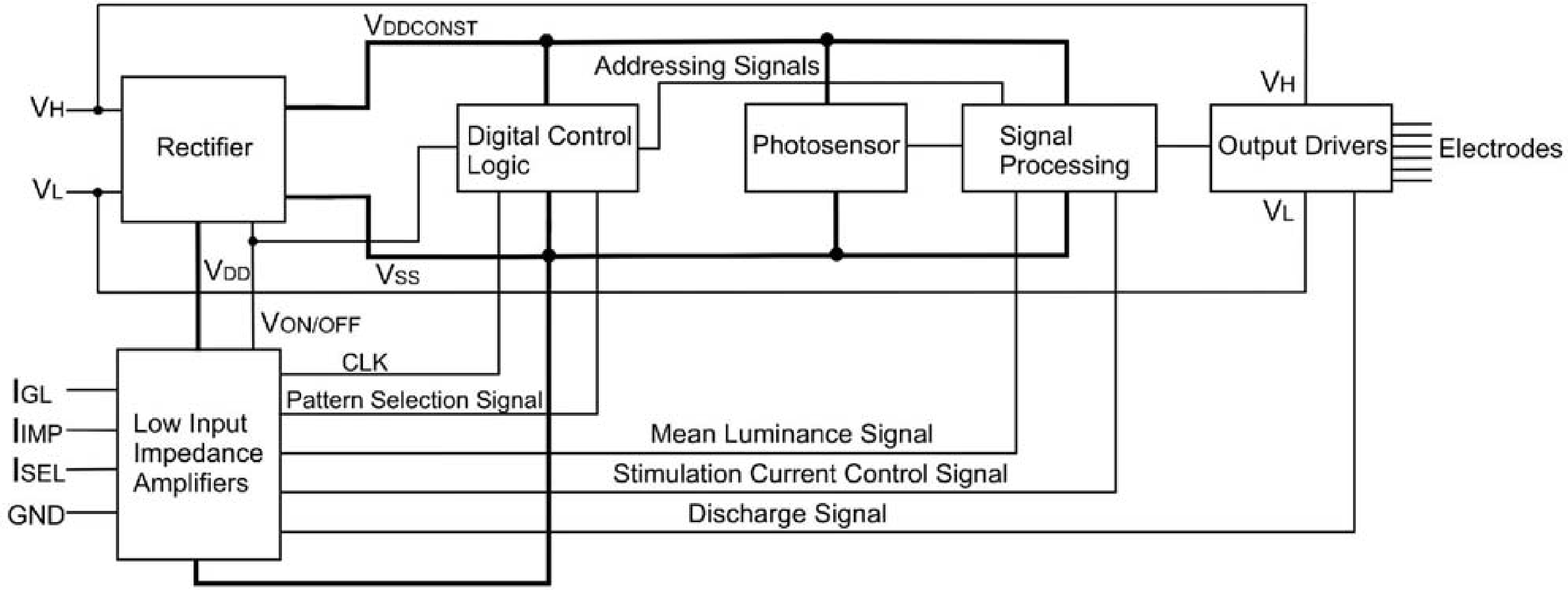
- Strength-duration stimulation curves



Sensitivity curves of 15 experiments with blind animal retina, responses of ganglion cells measured with loose clamp technique

Example of a retinal stimulation system

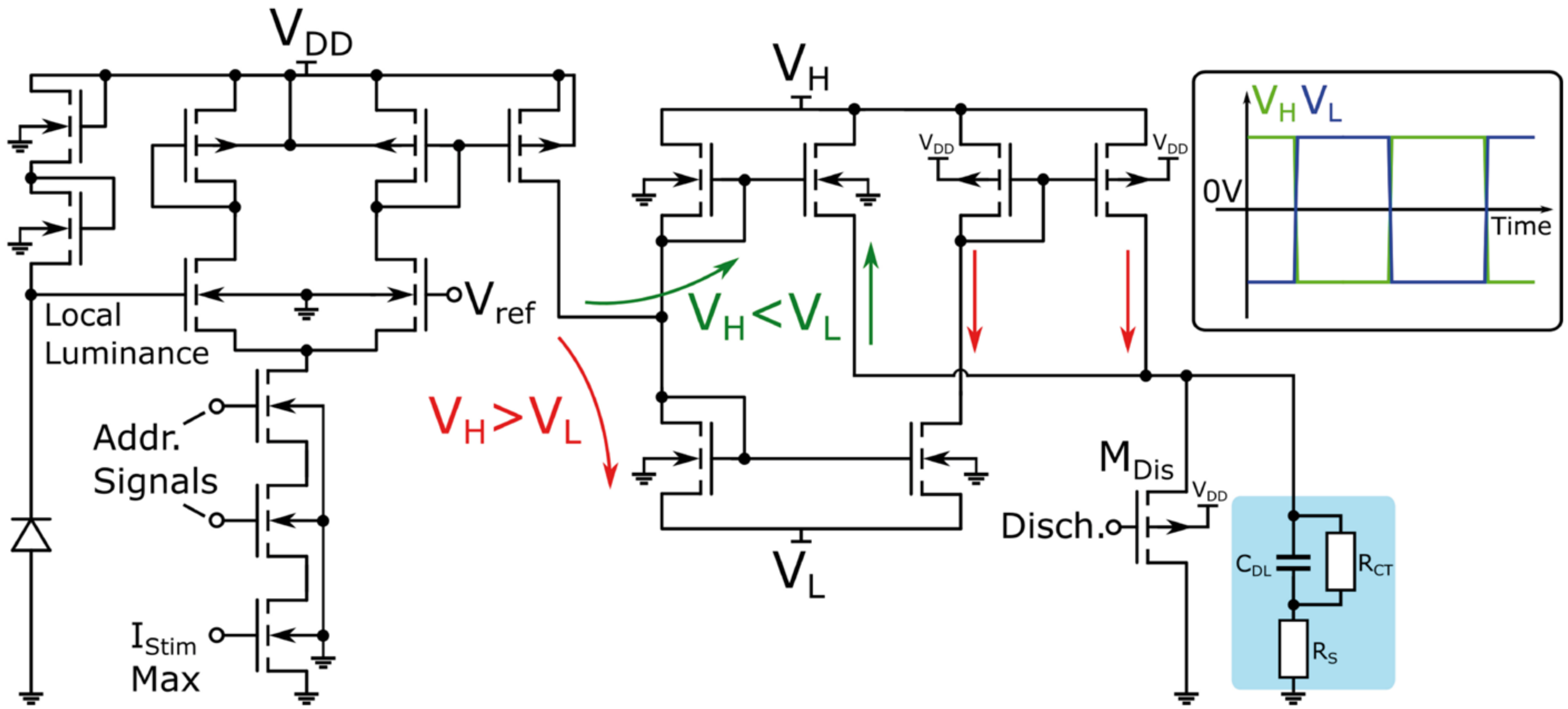
- 1600 stimulation sites, AC coupled implant



DC-free chip concept

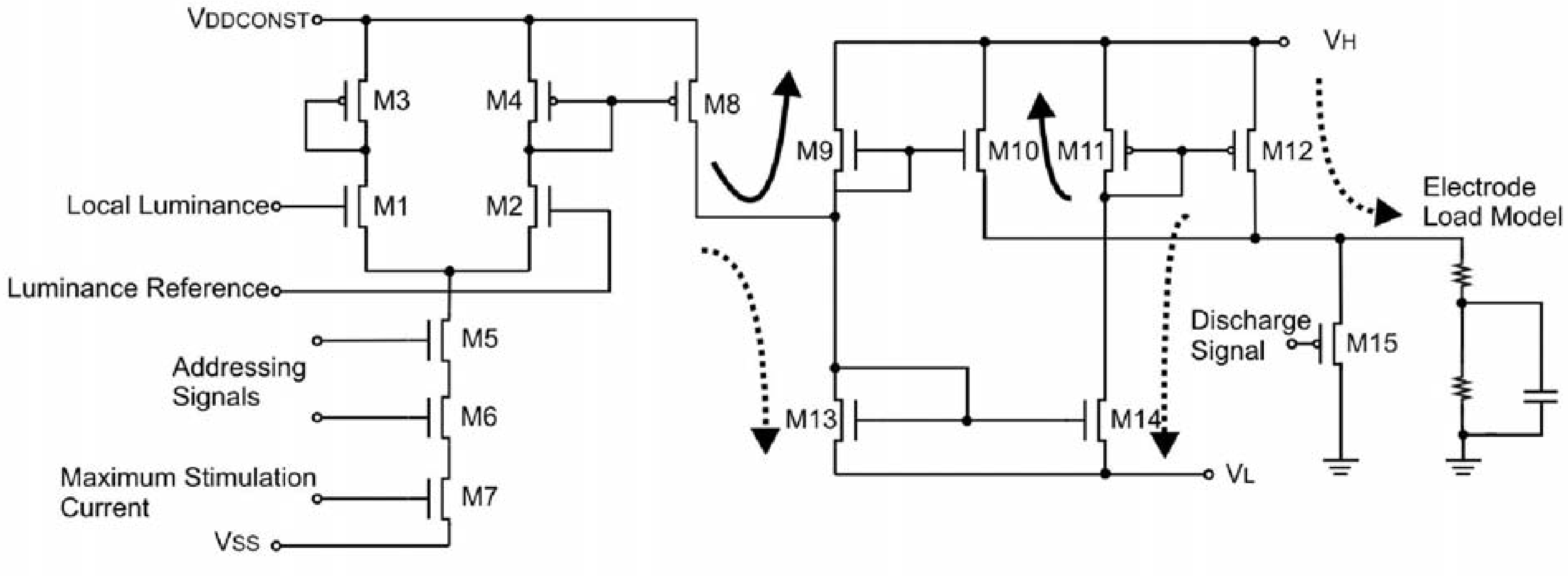
Example of a retinal stimulation system

- 1600 stimulation sites, AC coupled implant



Example of a retinal stimulation system

- 1600 stimulation sites, AC coupled implant



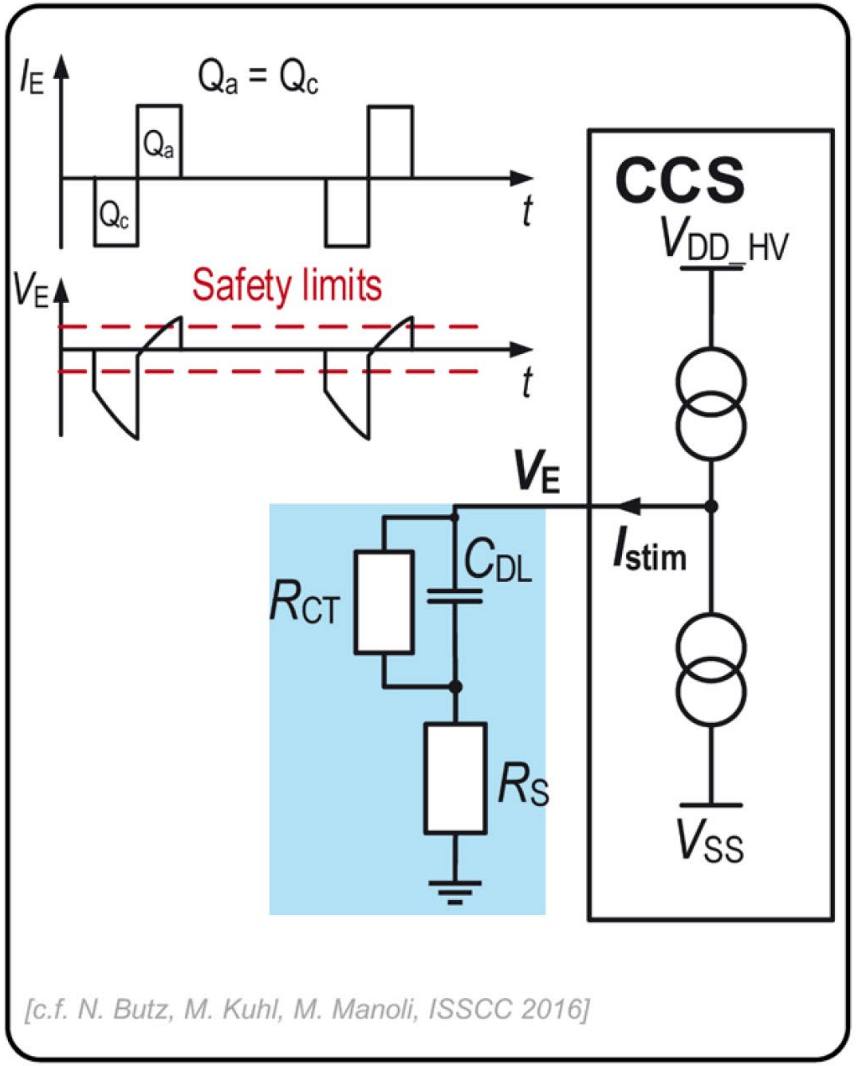
Low voltage drop AC electrode driver

Outline

- Electric stimulation and electrode interfaces
- Different types of stimulation
- Current stimulation: examples of circuit implementation
- Charge balancing

Charge balancing problem

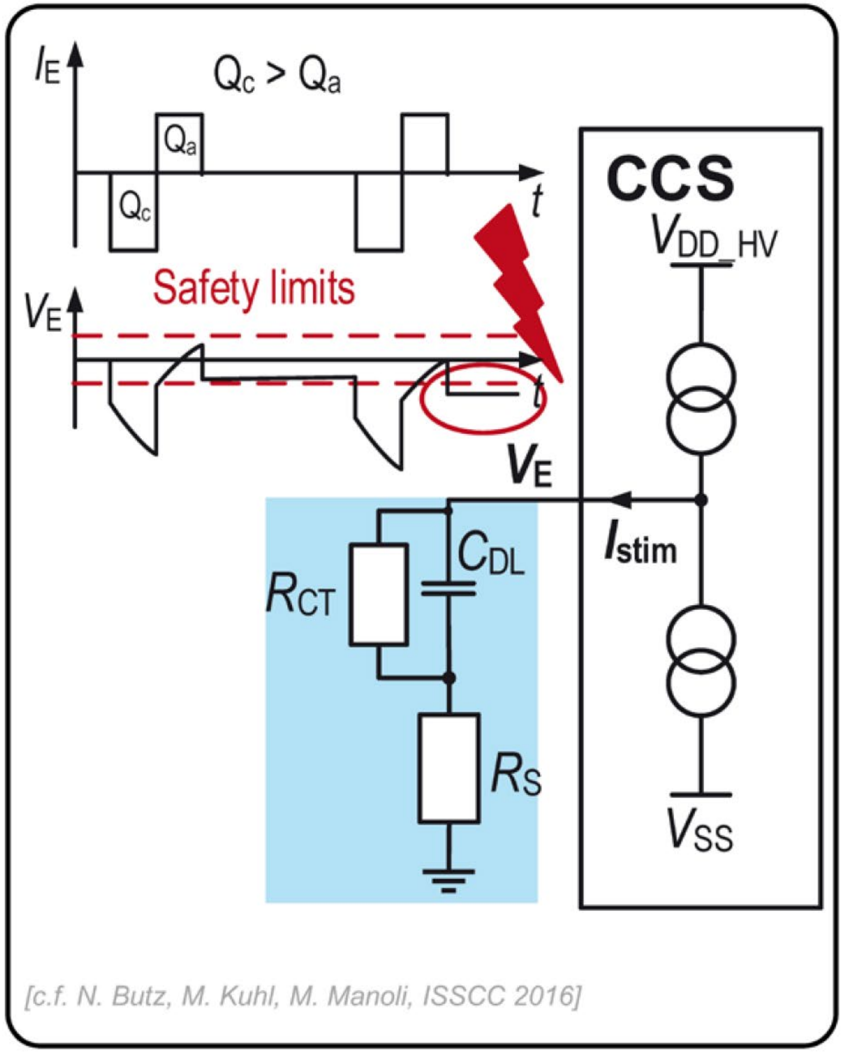
- Electrode potential V_E during bipolar current stimulation
- Charge balanced stimulation if: $Q_c = Q_a$
- No harmful DC voltage due to charge accumulation



M. Haas, M. Ortmanns: “Neural Stimulation Circuits” River Publishers, 2021

Charge balancing problem

- Results of unbalanced stimulation pulses
  - → excess voltage
  - → irreversible & toxic reactions
  - → tissue damage
  - → electrode corrosion



M. Haas, M. Ortmanns: “Neural Stimulation Circuits” River Publishers, 2021

Passive charge balancing

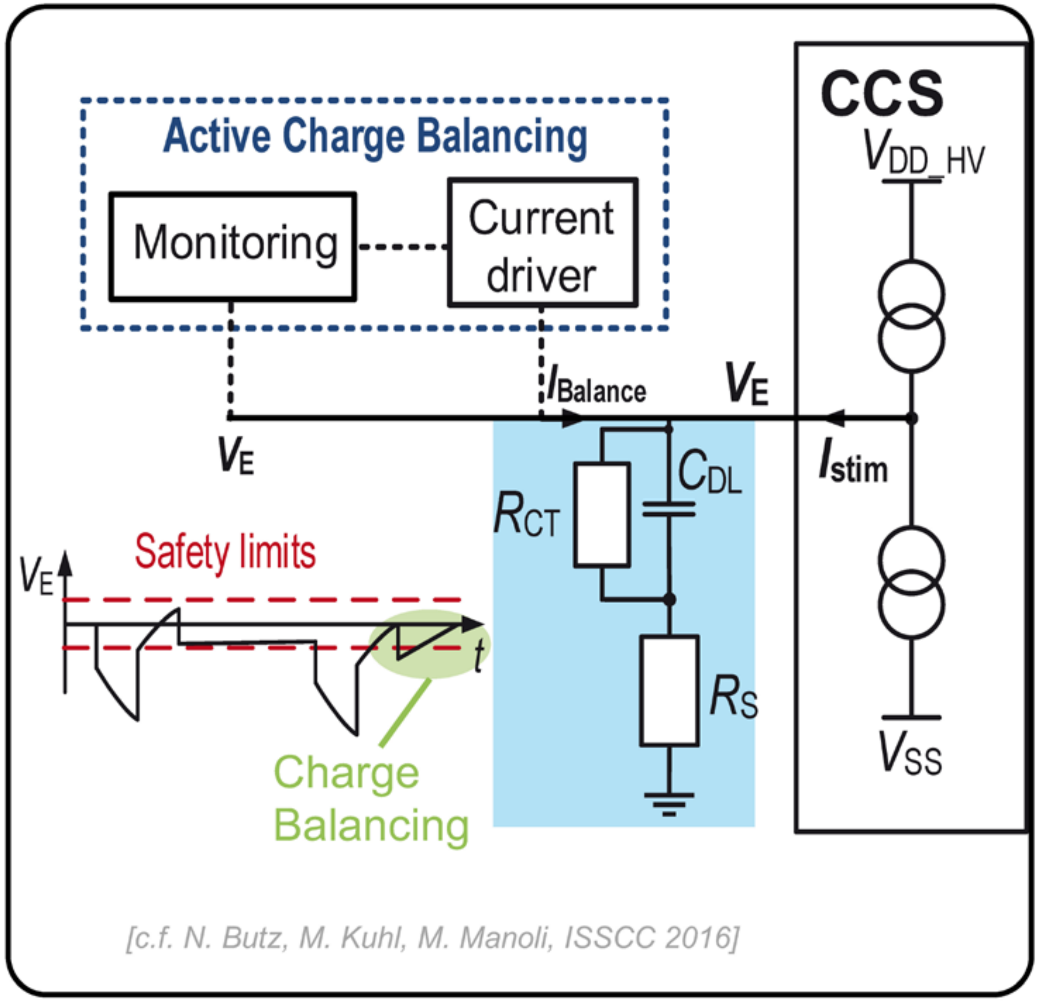
- **Biphasic pulses**
  ✗ process and mismatch variations
- **Blocking capacitor**
  off-chip – secondary protection
  ✗ no mismatch protection
  ✗ large size ($C_{block} >> C_H$)
  ✗ per channel
- **Passive charge balancing**
  Low (no) power, low area and most common
  ✗ settling behavior
  ✗ no monitoring of excess voltage

Use switch after each stimulation to short stimulation electrode to a common mode body potential

M. Haas, M. Ortmanns: "Neural Stimulation Circuits" River Publishers, 2021

Active charge balancing

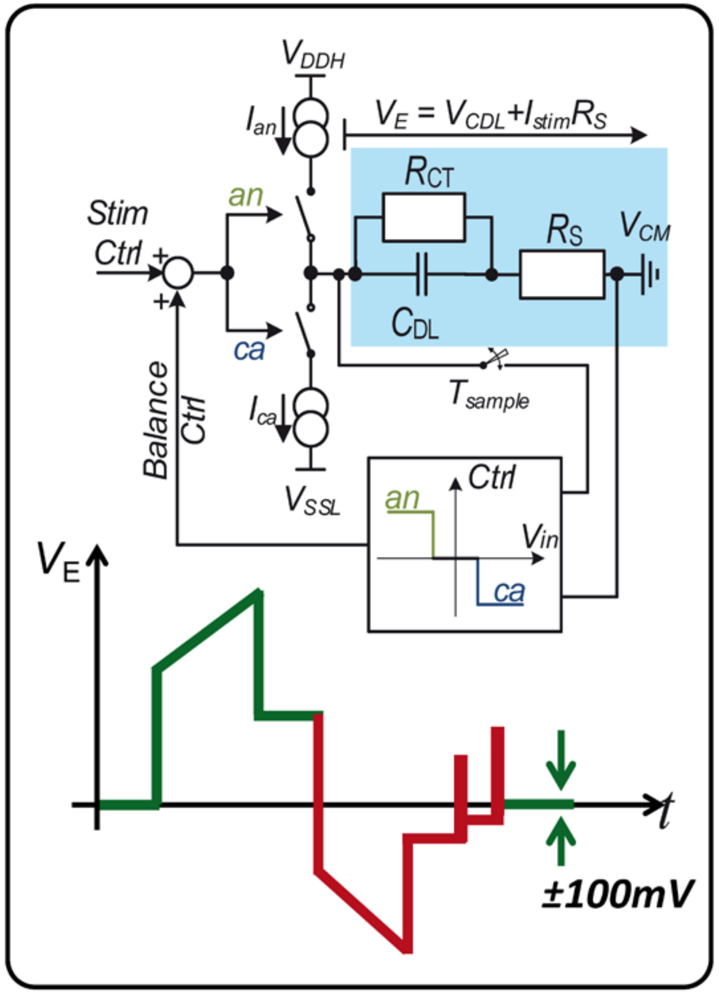
- When to monitor?
  - Continuously?
  - During I_{stim}=0 intervals?
- Current driver: Reuse?



M. Haas, M. Ortmanns: “Neural Stimulation Circuits” River Publishers, 2021

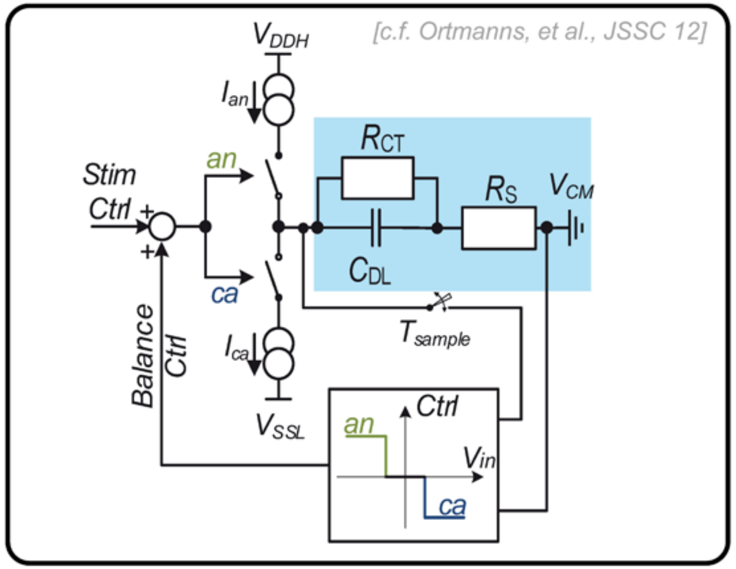
Active charge balancing

[c.f. Ortmanns, et al., ISSCC 06/07]



- Excess voltage outside stimulation
  - Spike insertion: balance after every stimulation
  - Offset based: balance over time

Measure V_{CDL} , not I_{Stim}*R_S
Reuse output stage for CB



M. Haas, M. Ortmanns: “Neural Stimulation Circuits” River Publishers, 2021

Exercise 1

- Why is charge balancing important?

Exercise 1: answer

- Because we must make sure that the DC current applied to the stimulation electrodes is zero.
- This avoids the risk of electrolysis and thus minimizes the risk to bring metal ions in the electrolyte (which are the body fluids of the patient)

Exercise 2

- Answer the following questions:
  a) Is stimulation always effective in eliciting action potentials?
  b) Is stimulation always safe?
  c) How large should be the charge transfer resistance in a safe implanted electrode?
  d) Why should we adapt voltage compliance to the current stimulation levels?
  e) To efficiently provide a variable supply level should we prefer LDOs or DC-DC converters?
  f) Show the current copier concept and discuss why it is more efficient than a conventional current mirror

Exercise 2: answer

- Answer the following questions:
  a) No, one must take input account for instance: polarity, strength (current levels, charge injected), distance from the electrode and stimulus duration
  b) Surely not, apart from the problems with DC current, which must always be avoided, excessive stimulation may result in tissue damage e.g. due to overheating
  c) For an implanted electrode, the exchange current i_o should be as close to zero as possible, to avoid ions being released in the body fluids even if no stimulation occurs. According to the equation in slide 18, this means that the charge transfer resistance should be ideally infinite in a safe implanted electrode
  d) To avoid a very large power consumption. Indeed, the dissipated power is equal to the stimulation current flowing times the voltage supply needed by the current stimulation circuit. If the supply is fixed to large values, needed when the current is large, to accommodate for large swings at the electrode input, when the stimulation currents are small the supply would stay large while the electrode input swing is small, and this would waste a lot of power. Better to lower the supply when small currents (and thus small voltage swings at the electrode input) are needed.
  e) The supply current in an LDO is the same as its output current. Thus, using an LDO would not help to improve efficiency by lowering the bias voltage when needed. The total power consumption would always stay the same, as the supply of the LDO stays the same and the LDO current too. A DC-DC converter, on the contrary, can provide lower power at the output by requesting lower current from its supply, and thus is efficient in generating a bias supply which is lower for lower currents – it will simply require smaller power. However, a DC-DC current output is typically noisy and thus an additional LDO must typically be added at the output of the DC-DC converter (!)
  f) The current copier is more efficient as it allows to duty-cycle the input current in the mirror (I_{ref} needs to be non-zero only till C_{mem} is charged)

Summary

- An electrode model including reversible potential, double layer capacitance, charge transfer and series electrolyte resistances has been introduced
- Different stimulation types are possible: voltage, current and charge. They have advantages and disadvantages.
- Current stimulation is very much used in recent papers. Examples of circuit implementations minimizing needed voltage supply are given.